STUDY OF SERUM MAGNESIUM LEVEL IN TYPE 2 DIABETES MELLITUS

Dissertation submitted in partial fulfilment of requirements for

M.D.DEGREE IN GENERAL MEDICINE

BRANCH I

Of

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CERTIFICATE

This is to certify that the dissertation entitled "**STUDY OF SERUM MAGNESIUM LEVEL IN TYPE 2 DIABETES MELLITUS**" is a bonafide work done by **Dr.SUBASH CHANDRABOSE G.** at Thanjavur Medical College,Thanjavur in partial fulfilment of the university rules and regulations for award of M.D., Degree in General Medicine (Branch-I) under my guidance and supervision during the academic year 2010-2013.

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ETHICAL COMMITTEE

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The Ethical Committee, Thanjavur Medical College has decided to inform that your Dissertation Topic is accepted and you are permitted to proceed with the above study.

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CONTENTS

SL.NO	TITLE	PAGE NO
1	INTRODUCTION	1
2	AIMS AND OBJECTIVES	3
3	REVIEW OF LITERATURE	4
4	METHODOLOGY	53
5	RESULTS	58
6	DISCUSSION	80
7	CONCLUSION	86
8	ANNEXURES	
	BIBLIOGRAPHY	
	ANNEXURE I -ABBREVIATIONS	
	ANNEXURE II- PROFORMA	
	ANNEXURE III-MASTER CHART	
	ANNEXURE IV- KEYS TO MASTER CHART	
	ANNEXURE V- CONSENT FORM	

STUDY OF SERUM MAGNESIUM LEVEL IN TYPE 2 DIABETES MELLITUS

ABSTRACT

BACKGROUND

A high prevalence of magnesium deficiency is reported in diabetics. Magnesium depletion has a negative impact on glucose homeostasis and insulin sensitivity in type 2 diabetic patients as well as on the evolution of complications such as retinopathy, nephropathy, neuropathy and arterial atherosclerosis. The aim of this study is to estimate the prevalence of hypomagnesemia in patients with type 2 diabetes mellitus and its correlations with microvascular complications of diabetes like retinopathy, nephropathy, neuropathy.

MATERIALS AND METHODS:

Patients with type 2 diabetes admitted in Thanjavur Medical College and Hospital over a period of one year between October 2011 to October 2012 formed the study population. The sample size was 100 patients. Serum magnesium concentration was measured by calmagite dye method.

RESULTS:

The study revealed that prevalence of hypomagnesemia in study subjects was 35%. Sex, age and duration of diabetes were not significant predictors of

serum magnesium. Significant association was found between hypomagnesemia and diabetic retinopathy, nephropathy, neuropathy. Significant correlations were not found with co morbidities such as ischemic heart disease and hypertension.

Low serum magnesium concentrations are common in type 2 diabetics. Magnesium deficiency is conclusively associated with diabetic retinopathy, nephropathy, neuropathy.

KEY WORDS:

Magnesium ,Diabetes Mellitus, Retinopathy, Nephropathy, Neuropathy

INTRODUCTION

India is frequently referred to as the diabetic capital of the world as it has the highest number of cases in the world.

In worldwide the last 2 decades, incidence is suddenly increased from 30 million cases in 1985 to 171 million in 2000. Recent data suggests that prevalence of DM by the year 2030 could be 360 million. DM is worldwide in distribution and the incidence of both types is rising.[1, 2]

The distribution of both T1 DM and T2DM varies worldwide, due to relative difference in genetic and environmental factors in different parts of the world. Recent data shows it is associated with 10-30% reduction of life expectancy, most common cause of blindness in the age group of 20 to 65 years, 25 fold increased risk of non traumatic lower limb amputations and increase incidence of end stage renal disease approximately 1000 patients per year[2].

India had around 31.7 million cases in year 2000 which is expected to rise alarmingly to around 79.4 million in 2030 by which time every fifth diabetic subject in the world would be an Indian[3].

In Tamilnadu the prevalence in 2008 is 18.6% in urban areas and 9.1% in rural areas[3].

Although DM can cause hypomagnesemia , low serum magnesium level is a risk factor for DM. Magnesium is an essential element for several enzymes

that play important role in glucose metabolism. Animal studies found that low magnesium has a negative effect on post receptor signalling of insulin. Some studies have also found that magnesium supplementation improves insulin action and glucose metabolism in diabetics[4].

Magnesium is involved in multiple levels of insulin secretion. Magnesium deficiency can modify the Na^+ K^+ ATPase channel that maintains sodium, potassium and glucose transport[5].

In DM there is a direct correlation between serum magnesium concentration in blood and cellular glucose disposal that is independent of insulin secretion.[6]

Low serum magnesium level has direct correlation with microvascular complications (retinopathy[7], neuropathy. nephropathy) and macrovascular complications (IHD and cerebrovascular disease)[8].

In elderly type2 DM Paolisso hypothesized that oral magnesium supplementation for 4 weeks results in decreased fasting blood sugar level increased plasma and RBC magnesium level.[9]

In this study serum magnesium concentration in type2 DM patients is correlated with occurrence of microvascular complications.

OBJECTIVES

The aims of this study are

1. Measurement of serum magnesium concentration in diabetes mellitus .
2. To estimate the prevalence of hypomagnesemia in patients with type 2 diabetes mellitus
3. Its correlation with microvascular complications like retinopathy, nephropathy, neuropathy.

REVIEW OF LITERATURE

DIABETES MELLITUS

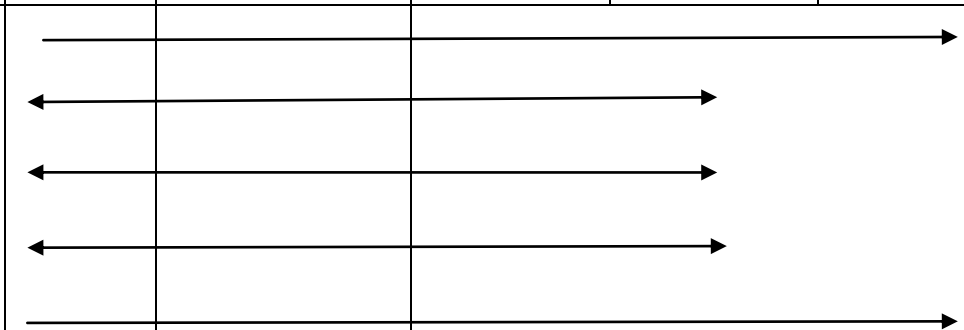
Diabetes Mellitus is a clinical syndrome characterized by high blood sugar level (hyperglycemia) and glycosuria due to relative or absolute deficiency of insulin secretion or its action, or insulin resistance that leads to disturbances in carbohydrate ,protein, fat metabolism , water and electrolyte homeostasis.

THE HISTORICAL ASPECTS

Its history has been characterized by numerous cycles of discovery, neglect and rediscovery. Its history may be divided into four major periods. The 'ANCIENT' period showed the first clinical features of DM and its complications. The 16 th to 18th centuries have been termed the 'DIAGNOSTIC' period, as DM was then identified as a separate disease entity. The mid to late 19th centuries may be consider as the first 'EXPERIMENTAL' period. During this period role of the pancreas became clear and the molecular level of diabetes were initially identified[10]. Finally, in the 20th century knowledge about diabetes is well known.

The word Diabetes in Greek means – "I run through Siphon". Indian name for Diabetes is Madhumeha – Honey in rain. In 16th century, Susrutha in the Sanskirit book of surgery, and Charaka in the Sanskirit book of medicine have mentioned about Diabetes. The first person -Vaidys – tested the urine of diabetic patients.

SPECTRUM OF DIABETES MELLITUS & GLUCOSE HOMEOSTASIS

Types	Normal glucose tolerance (mg/dl)	HYPERGLYCEMIA			
		PREDIABETES IFG & IGT (mg/dl)	DIABETES MELLITUS		
			NOT INSULIN REQUIRED	INSULIN REQUIRED FOR CONTROL	INSULIN REQUIRED FOR SURVIVAL
T1DM T2DM Other types GDM Time (years)					
FBG (mg/dl) 2-h PPBG (mg/dl)	< 110 < 140	110-125 140 – 199	≥ 126 ≥ 200		

ETIOLOGICAL CLASSIFICATION OF DIABETES

1. Type 1 Diabetes
2. Type 2 Diabetes
3. Specific types
4. Gestational Diabetes Mellitus (GDM)

SPECIFIC TYPES OF DIABETES

A. Genetic mutation in the β-cell function:

1. MODY - maturity onset diabetes of the young

Type1- Hepatocyte nuclear transcription factor 4α.

Type2 -Glucokinase.

Type 3 -HNF 1α .

Type 4- Insulin promoter factor 1.

Type5- HNF 1β.

Type 6- Neuro D1.

2. Mitochondrial DNA

3. Proinsulin or insulin conversion

B. Genetic mutations in insulin action:

1. Lipodystrophy syndromes

2. Leprechaunism syndrome

3. Rabson-Mendenhall syndrome

4. Type A insulin resistance

C. Diseases of the pancreas:

It includes pancreatitis, pancreatectomy, pancreatic malignancy, cystic fibrosis, etc.

D. Endocrine disorders:

Pheochromocytoma, somatostatinoma, aldosteronoma, etc.

E. Drugs:

Glucocorticoids, diazoxide, beta agonists, thiazide diuretics.

F. Infectious causes:

Rubella, cytomegalovirus, coxsackie virus.

G. Immune-mediated Diabetes:

Stiff-man syndrome and anti-insulin receptor antibodies.

H. Genetic syndromes

Myotonic dystrophy, porphyria, Prader-Willi syndrome. , Klinefelter's, Turner's and Down's syndrome.

GESTATIONAL DIABETES MELLITUS (GDM)[11]

It is the occurrence of reduced glucose tolerance during gestation.

Incidence: 7% (range 2–10%) of pregnancies.

Most women revert to normal euglycemia in postpartum period, but have a subsequent risk (35–60%) of developing diabetes mellitus in the next 10–20 years.

Effects of diabetes on pregnancy:

- Hydraminos
- Toxaemia of pregnancy
- Maternal infections
- Difficult labour
- Recurrent abortions
- Postpartum haemorrhage
- Puerperal sepsis.

Effects of diabetes on the foetus:

- Prematurity
- Still birth
- Macrosomia
- Postpartum hypoglycaemia
- Respiratory distress syndrome
- Hyperbilirubinemia
- Congenital heart disease
- Neural tube defects.

TYPE 1 DIABETES MELLITUS

Pathogenesis Of Type 1 Diabetes Mellitus:

Normal islet

⇩

?Viral infection in pancreatic beta cell

⇩

Secretion of IFN-α by pancreatic beta cell

⇩

Hyperexpression of MHC class1 antigen within beta cell

⇩

Insulitis

⇩

Insulin deficient islets

Immune Mediated Diabetes (Type 1A)

Its incidence is around 5-10% all diabetes. It occurs due to immune mediated destruction of pancreas.

Pathogenesis:

1. Genetic predisposition: Diabetogenic genes are located in short arm of chromosome 6
2. Environmental triggers
   a) Viral infections like rubella virus, CMV, mumps virus, etc.
   b) Toxins like pentamidine, streptozocin

Viruses and above agents directly act on beta cells and initiate autoimmune processes against these cells.

3. Immune mechanism

DM can occur with other autoimmune disorders. It is due to presence of diabetogenic peptide which triggers the immune system. .Antibodies against β-cells include

1. Islet cell auto antibodies,

2. Autoantibodies to insulin,

3. Autoantibodies to glutamic acid decarboxylase (GAD65) and

4. Autoantibodies to tyrosine phosphatases IA-2 and IA-2B.

Anyone of above auto antibodies present in 85-90% of patients.

Age of onset is usually less than 30 years. Usually associated with prominent muscle wasting. It has an abrupt onset with rapid progression course. Classical symptoms of diabetes like polyuria, polyphagia, polydipsia are present. Family history of diabetes mellitus is usually absent.

HLA DR3 or DR4 seen in>90% of patients. Pancreatic islet cells (of langerhans) almost destroyed and plasma insulin is low to absent. Plasma C peptide level is low. It is usually associated with other autoimmune diseases. Acute complications like diabetic ketoacidosis are very common. Insulin therapy is needed for survival and mortality is higher in untreated patients.

Idiopathic Diabetes (Type 1B)

These persons have absolute deficiency of insulin and are at risk of developing ketoacidosis. It is strongly inherited and there is no evidence for antibodies to beta cells. It is not associated with HLA.

TYPE2 DIABETES MELLITUS

90-95% of diabetics are Type 2 DM. Patients have insulin resistance and have relative deficiency of insulin. Specific aetiologies are not known. It usually starts after the age of 30 years. It has insidious onset, with gradual progressive course. Polyuria, polyphagia, polydipsia are not so classically seen as in type 1 DM. Family history of diabetes mellitus is usually present. No HLA links are seen. 50% concordance is seen in identical twins. Pancreatic islet cells are not totally destroyed .Plasma insulin in serum normal to high. Complications like hyperosmolar hyperglycaemic non ketotic coma are very often seen.

Risk of developing T2DM:

Age of onset of T2DM in proband (years)	Age corrected risk of T2DM for Siblings(%)
25-44	53
45-54	37
55-64	38
65-80	31

Pathogenesis of Type 2 DM:

1) Insulin Resistance

2) Pancreatic Beta Cell Failure

Insulin resistance:

Exact cause of insulin resistance is unknown. Possible mechanism is increase release of free fatty acids from adipose tissue that induce insulin resistance. In addition there is increased release of adipokines which act on receptors of insulin and dampen the action of insulin. There is a higher prevalence of insulin resistance is seen in metabolic syndrome.

Pancreatic Beta cell failure:

In the earlier stage of diabetes mellitus only moderate reduction of insulin secreting beta cells lost. At the time of diagnosis of type 2 DM more than 50% reduction of beta cell is seen. Most important pathological feature is the deposition of amyloid in pancreatic cells. There is no change in alpha cells but progressive destruction of beta cells leads to development of hyperglycemia.

Differences between Type 1 and Type 2 Diabetes Mellitus:

	T1DM	T2DM
Age of onset(years)	Less than 40	More than 50
Duration of symptoms	Usually weeks	Months to years
weight	Normal or decrease	Obese
Ketone bodies in urine	Present	Absent
Insulin requirement for survival	Needed	Not needed
Auto antibodies	Present	Not present
Diabetic complications at the time of presentation	Not present	Present
Family history	Uncommon	Seen in 25%
Other autoimmune disorders	common	Uncommon

Clinical features of DM

- Polyuria
- Increased thirst
- Dry mouth
- Nocturia
- Tiredness, lethargy, fatigability
- Visual defect

- Excessive weight loss
- Nausea, vomiting, headache
- Polyphagia
- Genital candidiasis
- Mood changes, irritability

Diagnostic criteria for Diabetes mellitus

It includes

A. Symptoms of diabetes plus random blood sugar ≥ 200 mg/dl

B. Fasting plasma sugar ≥ 126 mg/dl

C.2 hour postload plasma sugar ≥ 200 mg/dl during an oral GTT

D.HbA1C >6.5%

The new Diagnostic criteria for pre-diabetes and diabetes mellitus

FBS > 100 mg/dl = normal fasting glucose

FBS ≥100 mg/dl and <126 mg/dl =impaired fasting glucose (IFG)

FBS ≥ 126 mg/dl = provisional diagnosis of diabetes (on more than one occasion)

The corresponding categories when the oral GTT is used ,are as follows

2 h BS < 140 mg/dl = normal glucose tolerance

2 h BS ≥ 140 mg/dl and < 200 mg/dl = impaired glucose tolerance (IGT)

2 h BS ≥ 200 mg/dl = provisional diagnosis of diabetes (must be confirmed on subsequent day)

FBS-fasting blood sugar, 2 h BS- 2 hour post load blood sugar.

The prognostic significance and outcome are same whether it is the FBS >126 mg/dl or 2 hour postprandial blood sugar >200 mg/dl(in diabetes).The FBG test is now mostly performed because of ease of administration , convenience, acceptability to patients and its lower cost.

2-hour post load glucose is done by taking 75 g of glucose dissolved in 300 ml of water.

Fasting is defined as no food intake (i.e. overnight) for at least 8 hours. Random is defined as any time of day without regard to time since the last meal.

Screening for diabetes:

Diabetes is one of the diseases diagnosed late when multiple complications have appeared. Nearly 1/3rd of group remain undiagnosed. But no studies have supported screening of asymptomatic persons. But use of fasting blood sugar as a screening test for Type 2 DM is justified in individuals at high risk group.

Glycosylated haemoglobin C is also recommended for screening.

Adverse factors for Type 2 Diabetes Mellitus

1. Obesity
2. Family history of DM
3. History of diabetes mellitus during pregnancy (GDM) or Birth of baby weight > 4kg
4. HDL cholesterol level ≤ 35mg/dL or triglyceride level ≥ 250mg/dL

5. Race/ethnicity

6. Type A personality

7. Evidence of vascular disease features

Standards of medical care in DM

It is a chronic progressive disease that required frequent medical care for to decrease acute and chronic complications.

Initial Evaluation includes

- Detailed Medical history
- Previous HbA1C reports.
- Detailed history of dietary pattern, and weight history and any developmental delay in earlier age.
- Detailed history of prior treatment and present treatment of DM.
- Exercise history.
- Previous or present infections, particularly skin, foot, oral GIT and urinary tract infections.

2) Physical examination:

- Height, weight and body mass index
- Sexual maturation staging.
- BP measurement, including orthostatic measurements
- Examination of pulses
- Oral examination.

- Thyroid gland examination.
- Cardiac evaluation.
- Eye-fundoscopic examination
- Abdominal examination
- Hand examination.
- Foot examination.
- Dermatological examination (for tinea, acanthosis nigricans and insulin-injection sites).
- CNS examination.
- Examination for secondary causes of diabetes (e.g.hemochromatosis,pancreatic disease).

3) Laboratory evaluation

- HbA1C measurement
- Fasting serum lipid profile levels, which includes total cholesterol, HDL, Triglycerides, LDL, VLDL.
- Examination of micro albumin in urine in T1DM who have had duration of > 5 years and in all cases with T2 DM .
- Serum creatinine.
- Thyroid stimulating hormone (TSH) level in all T1DM, in T2DM with clinical features.
- ECG in adults, if clinically needed..

- Examination of urine for ketone bodies, protein and sediments.

4) Referrals:

• Ocular examination.

• Behavioural specialist.

• Podiatrist.

Goals to be achieved in Diabetes mellitus:

HbA1C < 7.0%

Fasting plasma sugar: 90 – 130 mg/dl

Post prandial plasma sugar: < 180 mg/dl

Blood Pressure :< 130/80 mmHg

LDL < 100 mg/dl

Triglycerides < 150 mg/dl

HDL> 40 mg/dl

Blood Sugar Control Goals- An Approach :

•Goals vary from person to person.

•Following persons (Children, Women who have conceived and older age) need special care.

•Less severe control is required in patients with recurrent episodes of hypoglycaemia.

•More adequate control of blood glucose (i.e. a normal HbA1c < 6%) may further reduce complications.

•Postprandial sugar may be targeted if glycosylated haemoglobin C levels are not met despite reaching fasting sugar level.

Complications of Diabetes Mellitus:

Diabetes has both acute and chronic complications.

Acute complications:

It includes

1.Diabetic ketoacidosis (DKA):

It is an acute medical emergency, characterised by

- Increase blood sugar
- Ketone bodies in serum and urine
- Metabolic acidosis

Complications:

- Cerebral edema
- Acute respiratory distress syndrome
- Disseminated intra vascular coagulation
- Thromboembolism
- Circulatory failure

2. Hyperglycemic Hyperosmolar state (HHS):

It is characterised by

- hyperglycemia without metabolic acidosis or ketone bodies
- thromboembolic manifestations are more common

3. Hypoglycemia:

- It is more common in insulin treated patients.

4. Lactic acidosis

Chronic Complications:

1.Diabetic Retinopathy

2.Diabetic Neuropathy

3.Diabetic Nephropathy

4.IHD

5. Cerebrovascular accident

Transient ischemic attack, stroke

6.Peripheral vascular disease

claudication, ischaemia

7. HT

8 . Infection like Tuberculosis, Candidaisis, Mucormycosis, Necrotising fasciitis, Periodontitis

9.Dupuytren's contracture

10 . Pseudogout

DIABETIC RETINOPATHY[12]

It is one of the commonest cause of blindness in adults in the age group30 to 65 years in developed countries. During the 1st two decades of disease, nearly all patients with T1DM and >60% with T2DM have retinopathy. 21 percent of T2DM patients have presented with retinopathy at first visit.

Classification:

Nonproliferative Diabetic Retinopathy (NPDR):

1. Mild type:

Presence of 1 micro aneurysm with one or more of the following :

- Retinal haemorrhage,
- Hard and soft exudates.

2. Moderate type:

- Presence of Haemorrhage/ micro aneurysms or
- Presence of both in at least one quadrant with one or more of the following:
- Soft exudates, venous beading and intra retinal microvascular abnormalities.

3. Severe type:

- Haemorrhage or micro aneurysms or
- Both in all quadrants,

- Venous beading in two or more quadrants , intra retinal microvascular abnormalities in at least one quadrant.

Proliferative Diabetic Retinopathy (PDR):

1. Early: One or more of the following:

a) NVE

b) NVD

c) Vitreous or preretinal haemorrhage

d) NVE< ½ disc area.

2. High risk: One or more of the following.

a) NVD > ¼- $^{1}/_{3}$ disc area

b) NVD with vitreous or preretinal haemorrhage

c) NVE > ½ disc area. Preretinal or vitreous haemorrhage.

3. Advanced PDR:

- High risk PDR, traction retinal detachment involving macula or
- Vitreous haemorrhage obscuring ability to grade NVD or NVE.

IRMA – Intraretinal micro vascular abnormalities.

NVE – Neovascularisation elsewhere.

NVD – Neovascularisation over the disc

Clinical features of Retinopathy

- Micro aneurysms
- Retinal haemorrhage

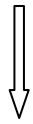
- Exudates
- Cotton wool spots
- Neovascularisation of retina and iris
- Subhyaloid haemorrhage
- Vitreous haemorrhage and fibrosis

Macular edema can occur at any stage of diabetic retinopathy. Non proliferative diabetic retinopathy usually appear at end of first decade or early second decade in cases of type2 diabetes mellitus. Proliferative diabetic retinopathy usually appears within 5 years of non proliferative diabetic retinopathy. Pregnancy, uncontrolled diabetes mellitus, uncontrolled HT can accelerate these changes.

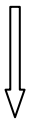
UKPDS study showed that strict sugar control(i.e. for every percentage of reduction of HbA1C) associated with a 35% reduction in risk of retinopathy[13], and strict BP control (to < 150/85 mmHg) results in 34% reduction[14]

Pathophysiology of microvascular complications:

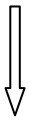
Increase glucose level



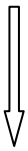
Activation of protein kinase c, Endothelial nitric oxide synthase uncoupling, Increase production of advanced glycation products, Activation of polyol pathway



Activation of reactive oxygen species



Increase oxidative stress



1.Altered gene expression

2.Decrease nitric oxide synthesis

3.Activation of protein kinase C

4.Increased formation of advanced glycation products

5.Induction of DNA damage

Other ocular complications :

- Cataract
- Glaucoma
- Retinal detachment
- Macular edema

Investigations for retinopathy:

- Visual acuity
- Fundus examination
- Fundus fluorescein angiography
- Slit lamp examination

Treatment options for retinopathy:

- Laser photocoagulation
- Injection of steroids
- Anti vascular endothelial growth factor

DIABETIC NEPHROPATHY

This is most common cause of stage five chronic kidney disease in world wide. Compared to type2 diabetes progression to chronic kidney disease is higher in type1 DM.

The diabetic nephropathy progresses from stage of microalbuminuria to stage of macroalbuminuria / clinical albuminuria to end stage renal disease. Progression from micro to macroalbuminuria usually taken upto 10-15 years.

ESRD develops in half of T1DM patients with clinical nephropathy within ten years and 3/4of patients by twenty years. But in type 2 DM, even after twenty years of overt nephropathy only 20% progress to ESRD.

Screening for Microalbuminuria:

A screening test should be done for urine microalbumin at the time of diagnosis in persons with T2 DM at the time of first visit , repeated after five years of disease duration. For patients with T1DM, test should be repeated yearly.

Screening for microalbuminuria can be performed by 3 ways.

1. Calculation of the albumin to creatinine ratio in a spot urine sample.
2. 24 hour Urine sample and measurement of albumin excretion.
3. Timed (e.g. 4 hr or overnight) collection.

24 hour collection urine sample is most reliable.

CATEGORY	Spot collection (μg/mg creatinine)	24 Hr collection (mg/24 hrs)	Timed collection (μg/min)
Normal	<30	<30	<20
Microalbuminuria	30 – 299	30-299	20-199
Macroalbuminuria	≥300	≥300	≥200

In addition microalbuminuria is the earliest feature of renal involvement, it is also as a independent marker of CAD.

DIABETIC NEUROPATHY

It occurs in almost half of cases with long duration of diabetes. The development of neuropathy is directly in correlation with the duration and degree of glycemic control[2,15].

Classification:

- Somatic
- Visceral or autonomic

Somatic:

1) Polyneuropathy

- Symmetrical mainly sensory and motor
- Asymmetrical mainly motor and proximal including amyotrophy

2) Mononeuropathy including mononeuritis multiflex

Visceral:

- Cardiovascular
- GIT
- Pupillary
- Genitourinary
- Sudomotor
- Vasomotor

Possible causes of neuropathy in DM includes

- Microangiopathy

- Formation of advanced glycation end products
- Increased level of protein kinase c
- Activation of polyol pathway leads to accumulation of sorbitol

Histopathology:

- Axonal degeneration of both myelinated and unmyelinated fibres
- Schwann cell basal lamina hypertrophy
- Patchy, segmental demyelination
- Basement membrane thickening and presence of microthrombi in neural vessels

The most common type reported is distal symmetrical sensory poly neuropathy. Most cases frequently presented with distal sensory loss, hyperesthesia, paresthesia and dysesthesia.

Painful neuropathies may also occur. It can be an acute (lasting < 12 months) and a chronic (lasting > 12 months).

Individuals with long standing T1 or T2 DM are prone to develop autonomic diabetic neuropathy.

Clinical features of Autonomic Neuropathy:

Cardiovascular features

- Orthostatic hypotension
- Fixed heart rate

- Resting tachycardia

Gastrointestinal features

- Dysphagia
- Nausea, vomiting, abdominal fullness
- Constipation
- Nocturnal diarrhoea

Genitourinary features

- Erectile dysfunction
- Urinary incontinence
- Recurrent urinary tract infections
- Retrograde ejaculation

Pupillary features

- Small pupil size
- Delayed response to light reflex

Sudomotor features

- Gustatory sweating
- Increased sweating in the night
- Anhidrosis and fissures in the feet

Vasomotor features

- Dependent edema
- Bullous formation
- Feet feel cold due to loss of vasomotor response

Tests for cardiovascular autonomic functions

1) Simple reflex test

A) Heart rate responses

- to valsalva manoeuvre (fifteen seconds): ratio of longest to shortest R- R interval Normal ≥1.21 ,abnormal≤1.20
- to deep breathing :6 breaths over 1 minute Normal ≥15 abnormal≤10
- to standing after lying :Ratio of R- R interval of 30^{th} to 15^{th} beats Normal ≥1.04 ,abnormal≤1

B) Blood pressure response to standing -Systolic BP fall Normal ≤10 abnormal≥30

C) Special Tests

- heart rate and BP in response to handgrip
- heart rate and BP variability using domain analysis of ambulatory monitoring
- MIBG scan of heart
- heart rate and BP variability using power spectral analysis of ECG monitoring

Diagnosis:

- Examination of the feet
- Look for ulceration,
- Ankle reflexes,

- Tuning fork using 128-Hz shows decreased vibration perception
- Semmes-Weinstein monofilament for pressure sensation
- Normal results on vibration testing (Likelihood ratio range, 0.33–0.51) or monofilament (Likelihood ratio range, 0.09–0.54) make large fiber peripheral neuropathy from diabetes less likely.
- Nerve conduction studies may show decreased conduction of the peripheral nerves.

MAGNESIUM

Magnesium is the 4th most abundant cation in the body. It is also the 2nd largest amount cation intracellularly, next to potassium. A normal adult has 21-28gms (approximately 2000mEq) of magnesium. Nearly 60% of total body magnesium is present in bone, 38% is in soft tissues with slightly higher concentrations in liver and skeletal muscle. (15-20 mEq/Kg). and less than 2% is present in extracellular compartment[16].

Serum concentration of magnesium varies from 1.7 to 2.4 mg/dL. The plasma concentration in healthy adults remain remarkably constant with very less fluctuations due to sensitive control mechanisms that are not fully understood

The mean daily oral intake of magnesium is roughly 25 mEq (140-360 mg/day). About 40% of the dietary magnesium is absorbed in the small intestine mainly the ileum. Elimination is mainly through kidneys and is about 100mg/day and it is well regulated. So when blood levels rise more than 2.4 mg/dl, magnesium excretion increases many folds. In event of magnesium loss absorption is increased dramatically, the main site being the thick ascending loop of Henle. Many factors inhibit reabsorption, like increased ECF volume, hypercalcemia, and use of thiazides.[17]

Biochemical importance of Magnesium:

Magnesium is an activator of critical enzyme systems that maintain cellular metabolism. The most important being the activation of enzymes that hydrolyze and transfer phosphate groups in the processes involving adenosine triphosphate (ATP). This ATP is essential for glucose catabolism as well as , lipid, amino acids, etc .

Magnesium is a cofactor for oxidative phosphorylation inside the mitochondria.

The macromolecular structure of DNA, RNA and ribosomes is maintained by magnesium.[18,19] It is also involved in protein synthesis by regulating the attachment of mRNA to the 70s ribosome.[20]

Regulation of Serum Magnesium

A) Renal regulation:

Renal regulation of serum magnesium concentration is mainly by altering its reabsorption at the thick ascending loop of Henle. Magnesium reabsorption is increased by parathyroid hormone and is reduced by hypercalcemia and hypermagnesemia

B) Intestinal absorption :

Intestinal magnesium absorption mainly at jejunum and ileum is increased by 1,25 $(OH)_2$ Vitamin D

C) Hormonal factors[23]

Increasing serum magnesium,

- Parathyroid hormone
- Glucagon
- 1, 25$(OH)_2$ Calcitriol.

Decreasing serum magnesium,

- Aldosterone
- Vasopressin (ADH)
- Thyroxine
- Calcitonin

Selected Food Sources of Magnesium[22] -Magnesium content in mg/100gm)

Nuts

- Almonds – 315
- Cashews – 260
- Peanuts – 175

Legumes

- Split Beans – 50
- Soyabean – 86

Fruits

- Dates – 35
- Banana – 30
- Oranges – 10
- Apple – 5

Dairy Products

- Milk – 24
- Butter – 20
- Yoghurt – 12

Cereals

- Shredded Wheat -110
- Rice – 40

Meat and fish

- Pork – 22
- Chicken – 21

- Beef – 18
- Fish – 22

Hypermagnesemia :

Hypermagnesemia is very uncommon in the absence of renal insufficiency, kidneys can excrete huge quantities of magnesium when needed (up to 250 mmol/d).[24]

Causes of hypermagnesemia

A) Impaired magnesium excretion

- Renal failure
- Familial hypocalciuric hypercalcemia

B) Excessive magnesium intake

- Cathartics
- Antacid preparations
- Parentral magnesium administration (eg.magnesium sulfate in PIH)

C) Rapid magnesium mobilisation from soft tissues

- Trauma
- Extensive burns
- Shock, sepsis
- Post-cardiac arrest

D) Other disorders

- Adrenal insufficiency
- Hypothyroidism
- Hypothermia

Clinical features:

The most important clinical presentation of hypermagnesemia are vasodilation and neuromuscular blockade, occurring at concentrations > 4.8 mg/dL (>2mmol/L). Hypotension usually does not respond to intravenous fluids and vasopressors.

Lethargy and weakness may progress to respiratory failure, paralysis and coma with depressed deep tendon reflexes occurs at serum magnesium levels > 4 mmol/L). Paralytic ileus may occur.

Prolongation of PR, QRS intervals, heart blocks and asystole occurs at serum magnesium levels around 10 mmol/L.

Treatment of Hypermagnesemia:

Generally involves recognising and removing the magnesium source Vigorous intravenous fluids and hemodialysis are necessary at times. Intravenous calcium in doses of 100-200 mg over 1 to 2 hrs provides a short term improvement

Hypomagnesemia :

Hypomagnesemia means a significant decrease in body magnesium stores (0.5 to 1 mmol/Kg). . Dietary magnesium deficiency is uncommon except in persons consuming alcohol.

Causes of Hypomagensemia[24]

I.Impaired intestinal absorption

A.Primary infantile hypomagnesemia

B.Malabsorption syndromes

C.Vitamin D deficiency.

II.Increased intestinal losses

A.Protracted vomiting / diarrhoea

B.Intestinal drainage, fistulae

III.Impaired renal tubular reabsorption

A.Genetic magnesium wasting syndromes.

1.Gitelman syndrome

2.Bartter syndrome

3.Na-K ATPase g-subunit mutations

B.Acquired renal disease

1.Tubulointerstitial disease

2.Post obstruction /ATN (diuretic phase)

3.Renal transplantation.

C.Drugs

1.Ethanol

2.Diuretics (loop, thiazide and osmotic)

3.Cisplatin, cyclosporine

4.Aminoglycosides, Amphotericin B

IV.Metabolic causes

1.Hyperaldosteronism

2.SIADH

3.Diabetes mellitus

4.Metabolic acidosis

5.Hypercalcemia

6.Hyperthyroidism

V.Others

1.Pancreatitis

2.Excessive sweating

3.Osteoblastic metastases

Many genetic/hereditary magnesium losing conditions are described , but are exceedingly rare. Prolonged nasogastric aspiration, intravenous fluids, infectious diarrhoea, fat losing enteropathies and inflammatory bowel disease may produce hypomagnesemia.[23] Magnesium deficiency is quite frequent in patients receiving loop diuretics like Furosemide.[24]

Incidence :

Hypomagnesemia is a relatively common electrolyte imbalance seen in around 12% of in- patients.[25] .In intensive care settings incidence is very high (60%).Parentral nutrition, diuretic usage, decreased serum Albumin levels , and aminoglycosides may be responsible for this high frequency[26]

Risk of incidence:[27]

- 2% in common people.
- 10 - 20% in hospitalized patients.
- 60-70% in ICU settings.
- 30 - 80% in Alcoholics.
- 25% in diabetic patients.

Hypomagnsemia occurs equally in males and females.

Clinical features:[28]

The clinical features appear only when serum magnesium concentrations are <1.2 mg/dL (0.5 mmol/L). It is presented as irritability, Central nervous system hyper excitability, and arrhythmias.[29]

History :

History concerned with hypomagensemia are usually nonspecific. They present with weakness, muscular cramps / palpitations. Sometimes abnormal behaviour in the form of irritability, apathy, psychosis, may be seen in severe cases. In few vertigo, incoordination, depression, or fits may occur.

Physical signs :

- Exaggerated deep tendon reflexes.
- Trousseau and Chvostek sign
- Difficulty in swallowing due to esophageal hypomotility
- Altered mental status
- Ataxia, nystagmus or seizures (at levels <0.8 mg/dl)
- Pulses may be irregular due to VPCs

ECG :

Hpomagnesemia can produce non specific alterations in the electrocardiogram. Mild to moderate hypomagnesemia (1.2 to 1.7 mg/dl) producing widened QRS complexes with tall T-waves. Severe Hypomagnesemia (<1.2 mg/dl) produces increased PR interval, broad QRS complex, flattening / T wave inversion and prominent U waves.[30]

Cardiac arrhythmias including sinus tachycardia, other supraventricular tachycardia and ventricular tachyarrhythmia also can occur.

Investigations:

Serum magnesium levels are estimated by several methods.

- Neutron activation analysis
- Atomic absorption spectrometry
- Ion selective electrodes (ISE)
- Equilibrium dialysis
- Calmagite dye method.

Calcium, potassium and phosphorous levels must be assessed. BUN and creatinine levels And Blood glucose levels should also be measured.

Treatment of Hypomagnesemia:

The route of magnesium replacement is according to severity of the clinical manifestations. Moderate to severe manifestations like patients with tetany or ventricular arrhythmias require 50 mEq of intravenous route slowly over 8 to 24 hours and repeated as and when needed to maintain concentration above 1.0 mg/dl.[31]

Oral replacement (magnesium chloride & Magensium lactate) should be given in patients with milder presentations. The background cause should be corrected.

Hypomagnesemia and other diseases:

A) Magnesium and cardiovascular diseases[32]

Arrhythmias can be precipitated in hypomagnesemia especially in acute coronary syndrome, cardiac failure and associated hypokalemia.

Torsade De pointes is a fatal arrhythmia precipitated by drugs that increase QT interval, electrolyte imbalance (low potassium and magnesium), or a decrease heart rate. Intravenous magnesium is recommended for this fatal condition.

Trials show significant correlation with ischemic heart disease. decreased level of serum magnesium is associated with higher incidence of ischemic heart disease.[39] The underlying mechanism for the increased risk is not fully understood.

Magnesium supplementation may improve the exercise tolerance, antithrombotic effect with aspirin and thus improves outcome in individuals with ischemic heart disease.[40]

Acute MI(myocardial infarction) is often associated with significant reduction in serum magnesium levels.[41] Hypomagnesemia associated with acute MI is probably responsible for increase in the frequency of fatal arrhythmias in the acute period.[33]

A positive correlation is seen in patients with hypomagnesaemia and CCF .It occurs due to use of diuretics. Whether this is associated with increased mortality is not known.[41]

B) Hypertension

Magnesium has significant role in controlling BP.[35] Hypomagnesemia leads to increased intracellular potassium and calcium levels which leads to vasoconstriction and increased peripheral vascular resistance. Magnesium may also have some direct effect on vascular smooth muscle.[36]

Studies have also found that requirement of anti hypertensive dosage is more in patients with low serum magnesium levels.

As per JNC recommendation high magnesium rich diet is necessary for prophylaxis and treatment of hypertension.[37]

C) Stroke

Studies have also found that increased magnesium intake decreases incidence of stroke.[42]

D) Osteoporosis

There is a significant correlation between serum magnesium levels and bone mineral density.[43]

E) Asthma:

Normal functioning of lung requires magnesium rich diet. There is a significant correlation between hypomagnesemia and incidence of bronchial asthma.

F) Dyslipidemia

Hypomagnesemia is associated with increased plasma LDL, cholesterol and triglyceride and reduced HDL.[44]

MAGNESIUM AND DIABETES MELLITUS

Magnesium is a essential element for metabolism of carbohydrate . 25 to 39% diabetes mellitus patients have hypomagnesemia

The clinical implications of magnesium deficiency in diabetes are many. Hypomagnesemia can be a result of hyperglycemia and can produce or increase insulin resistance. Hypomagnemia is implicated in the development of diabetic retinopathy. most often higher incidence occur if associated with hypertension,[38] thrombotic tendency,[45] insulin resistance[46] and the Reaven – Modan syndrome, a unique clinical entity that connects diabetes mellitus, hyperinsulinemia, hypertension and increased thrombotic tendency – all producing adverse cardiovascular outcomes.[47]

Causes of Hypomagnesemia in Diabetes Mellitus :

Initially, the cause of hypomagnesemia in diabetes was supposed to be due to

(1) Osmotic renal loss from glycosuria.

(2) Impaired absorption from GIT .

(3) Insulin mediated transfer of magnesium to RBC.

Recently a specific tubular defect has been suggested which results in hypermagnesuria. The exact site of this defect is not yet been identified. Insulin

treatment has been shown to reduce magnesium losses through kidneys. Garland[48] suggested that delay in insulin treatment is less effective in correcting the renal magnesium losses, probably due to certain irreversible changes.

The role of magnesium in Insulin Action :

Magnesium is a essential cofactor for insulin secretion, and activity. Hypomagnesemia decreases insulin secretion by the pancreas.[49]

Multiple studies have shown hypomagnesemia to increase insulin resistance. This insulin resistance is a post receptor defect and may be associated with calcium mediating the signal for insulin action.[46] Number of studies have shown that tissue response to insulin is more in the presence of magnesium.

In a recent study, the cellular uptake of magnesium, was shown to be reduced in diabetics.[50] there is also some proof that low magnesium levels directly produces insulin resistance. Nadler et al.[56] analysed 16 non diabetic individuals and found decreased insulin sensitivity after production of magnesium deficiency.

Similarly elderly non diabetic individuals had improved glucose tolerance, when subjected to magnesium supplementations for 4 weeks.[51] In non diabetic

obese subjects, insulin resistance was found to be associated with low magnesium levels, compared to non obese individuals.[52]

Tonyai, et al.[53] suggested that a low erythrocyte magnesium content can change membrane viscosity, and impair the binding of insulin with its membrane. Paolisso, et al.[51] were able to rectify the altered erythrocyte microviscosity with long-term magnesium supplementation.

Role of magnesium deficiency in diabetic end organ damage:

Magnesium deficiency is associated with diabetic microvascular disease. Hypomagnesemia has been shown in patients with diabetic retinopathy, with still lower magnesium levels in severe diabetic retinopathy. Magnesium depletion is also related to development of diabetic polyneuropathy. Corsonello, et al have suggested a relationship between diabetic microalbuminuria and serum ionized magnesium levels. Magnesium depletion also has been associated with multiple macrovascular complications.[43,50]

Grafton, et al[57] have suggested on the inositol transport theory for the development and progression of diabetic complications. According to this theory hyperglycemia leads to excessive stimulation of aldose reductase causing high cellular level of sorbitol. This sorbitol inhibits transport of inositol, thus decreasing intracellular inositol. The data of Grafton, et al show that

hypomagnesaemia causes a decrease in the affinity of the inositol transport protein for inositol, leading to a two fold reduction in rate of inositol transport and accelerated development of diabetic complications.

Resnick proposed that the 'primary' defect is the abnormal cellular ion handling leading to complications[47]

There is a significant correlation between magnesium and antioxidant levels. Weglicki, et al have hypothesized that a fall in magnesium level leads to loss of cellular activity against oxidative substances. Magnesium deficiency has also been shown to lower the efficiency of substances acting againt oxidants such as glutathione, vitamin c and Tocopherol.

Evidence for efficacy of Magnesium Supplementation in Diabetes Mellitus:

There is strong evidence that repletion of magnesium can reduce the insulin resistance, platelet reactivity and other cardiovascular risk factors .[54]

In a study involving 16 diabetics and 30 healthy controls, oral supplementation with magnesium hydroxide (250mg twice daily) resulted in reduced insulin requirements in the diabetic patients. Paolisso,[51] et al demonstrated magnesium supplementation given resulted in lower fasting plasma glucose levels, increased plasma magnesium levels and a significant improvement in β-cell response to glucose.

In type 2 diabetics, oral supplementation of magnesium decreases platelet reactivity, and decreases the incidence of hypertension and improves lipid profile.[44]

Clinical approach to Magensium Supplementation in Diabetes Mellitus

Diabetic patients at risk for hypomagnesemia such as ACS, DKA, chronic alcohol intake, prolonged duration of parentral therapy, chronic diarrhoea , diuretic therapy should have their magnesium levels measured.

Overt serum hypomagnesaemia should always be corrected. If hypomagnesemia is clinically suspected, but not supported by serum levels, a further test with erythrocyte or platelet magnesium concentration is mandatory

Magnesium chloride is the preparation of choice. Doses vary from 100 to 600mg/day .[54] Diarrhoea is the most important and the dose limiting side effect. Renal insufficiency with Glomerular filtration rate of less than 30 ml/min is the only factor that requires withholding dietary supplementation.

METHODOLOGY

SOURCE OF DATA

Patients with type 2 diabetes admitted in THANJAVUR MEDICAL COLLEGE & HOSPITAL, THANJAVUR, who satisfied the inclusion criteria and consented to participate in the study were included.

PERIOD OF STUDY

October 2011-October 2012

TYPE OF STUDY

Cross sectional study

100 patients were randomly selected of which 50 were males and 50 were females. Cases with renal failure, Acute Coronary Syndromes, patients on diuretics, alcoholics or with malabsorption were excluded. None were taking magnesium supplements or magnesium containing antacids. Informed consent was obtained.

INCLUSION CRITERIA

All patients both males and females above 13 years of age group with type 2 diabetes mellitus admitted in Internal medicine units of Thanjavur Medical College & Hospital, Thanjavur.

EXCLUSION CRITERIA

1. Patients with chronic renal failure.
2. Acute myocardial infarction in last 6 months.
3. Patients on diuretics.
4. Patients with history of alcohol abuse.
5. Patients receiving magnesium supplements or magnesium containing antacids.
6. Malabsorption or chronic diarrhea.
7. Age<13years.

DATA COLLECTION

The 100 diabetics (50 Men & 50 Women) were included in the study. Detailed history – including duration of diabetes, treatment mode, symptoms suggestive of diabetic neuropathy, associated diseases such as hypertension and ischemic heart disease was obtained as per the proforma.

Detailed physical and neurological examination was done. Retinopathy was assessed by direct opthalmoscopy.

Samples were collected for estimation of fasting blood glucose and magnesium level. Postprandial blood sugar was measured two hours after a standard meal. Nerve conduction study was done on selected patients by

experience neurologist with symptoms & signs suggestive of neuropathy. Blood urea, serum creatinine and 24 hour urinary albumin were estimated. Serum magnesium was estimated by Calmagite dye method. HbA1C measurement done by a modified calorimetric method.

CALMAGITE DYE METHOD – TEST PRINCIPLE

Under alkaline conditions, magnesium combines with calmagite dye to form a red colour which is read spectrophotometrically at 530 nm. Formation of colour is depends on magnesium levels. To eliminate the interference of calcium during estimation, EDTA is included in the reagent. Cyanide reduces heavy metal interference. Surfactant reduces protein interference.

TEST PROCEDURE

Three test tubes labeled Blank, Standard and Test are prepared as in table.

In test tubes	Blank	Standard	Test
Calmagite	1 ml	1 ml	1ml
Standard sample	-	10 ml	-
Patient's sample	-	-	10 ml
Distilled water	10 ml	-	-

This test tubes are incubated at room temperature (22-28ºC). The absorbance of Test (A_T), Standard (A_S) and Blank (A_B) are read at 530nm in spectrophotometer. Magnesium concentration is calculated by the following formula.

Magnesium concentration (mEq/L) = $(A_T-A_B / A_S-A_B) \times 2$

Serum magnesium concentration is expressed in mg/dl by linearity of 1 mEq/L = 1.2 mg/dl.

According to magnesium levels patients were classified into:

1) Normal, 1.7 to 2.4 mg/dl,

2) Low <1.7mg/dl,

3) High >2.4 mg/dl.

Patients were also categorized on the basis of duration of diabetes, presence of ischemic heart disease or hypertension, mode of treatment, presence/absence of retinopathy, neuropathy and nephropathy, and glycemic control (FBS and HbA1C).

Cases with diabetic retinopathy were further divided into

a) Nonproliferative diabetic retinopathy.

b) Proliferative diabetic retinopathy.

Diabetic nephropathy was graded depending on 24 hour urinary excretion of albumin as follows:

No nephropathy, < 30mg/24hour.

Microalbuminuria 30 – 299mg/24hour

Macroalbuminuria (clinical proteinuria) >= 300 mg/24hour.

STATISTICAL ANALYSIS

The statistical analysis was done by SPSS 15 software.MS Word and Excel were used to generate tables and charts. Following tests were used:

1. Chi square test
2. Student T test
3. Oneway ANOVA test

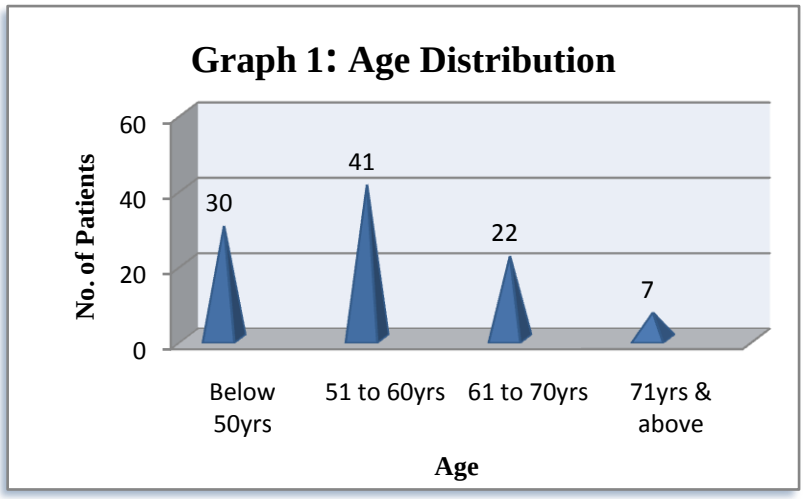
Statistical results were considered significant at P <.05

RESULTS

100 cases of type 2 DM (50 males, 50 females, mean age 56.87 years) comprised the study group.

Table 1: Age Distribution

Age (in years)	No. of Patients (n=100)
Below 50yrs	30
51 to 60yrs	41
61 to 70yrs	22
71yrs & above	7

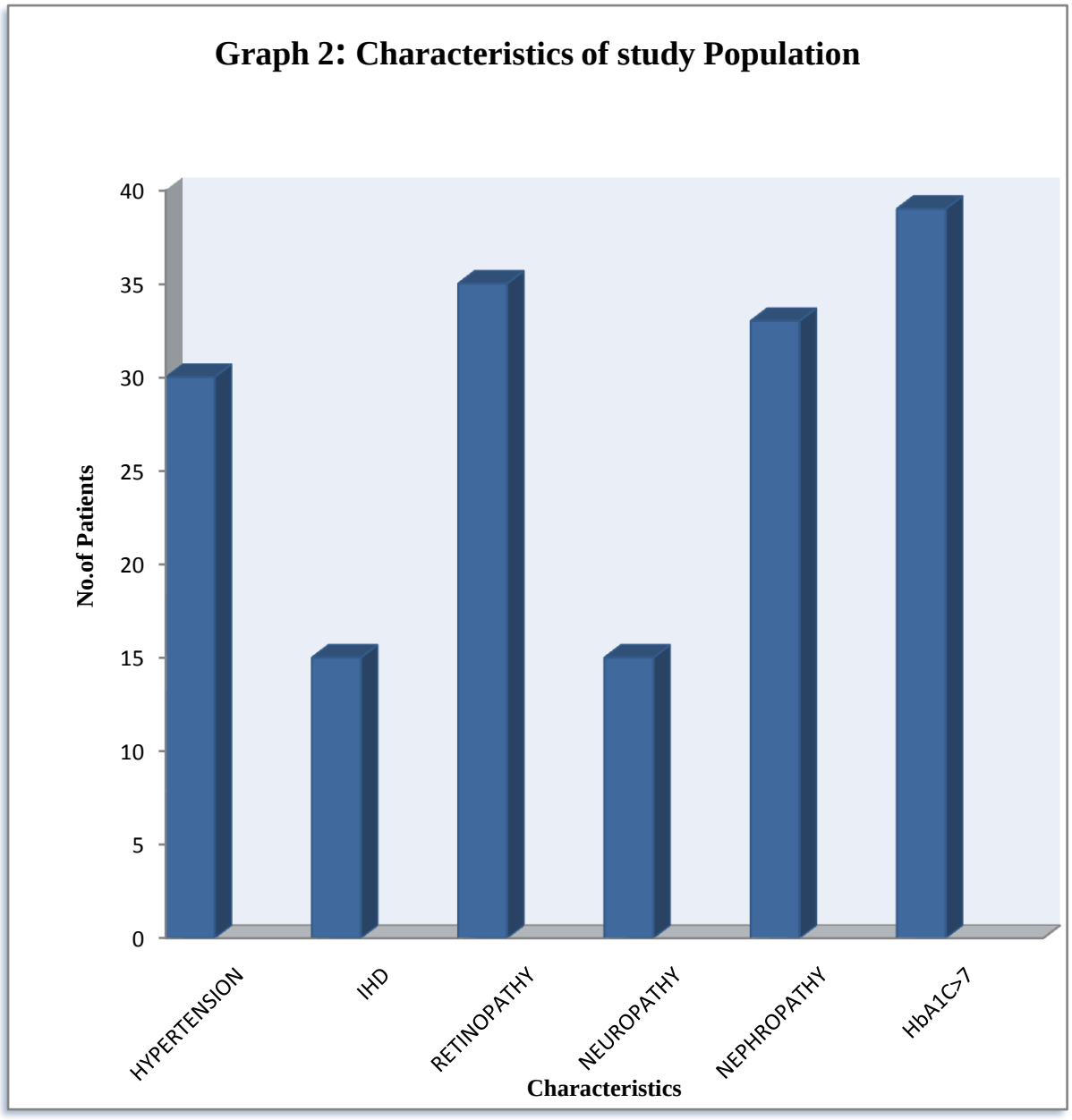


Patients were distributed across the age spectrum of 42 to 78 years. Mean age 56.87 years. Most patients (n=41) were present in 51-60 group. Youngest patient was 42 years old.

Table 2: Characteristics of study population

Characteristics	
No. of subjects	100
Age (Years)	56.87 (42 – 78)
Men	50
Women	50
Duration of diabetes (years)	8.89(2-23)
Medication	
Oral hypoglycemics	67
Insulin and oral hypoglycemics	33
Diet only	0
Comorbidities	
Hypertension	30
Ischemic heart disease	15
Diabetic retinopathy	
NPDR	33
PDR	2
Diabetic neuropathy	15
Diabetic nephropathy	
Microalbumineria	29
Macroalbumineria	4
Poor glycemic control	39

Graph 2: Characteristics of study Population



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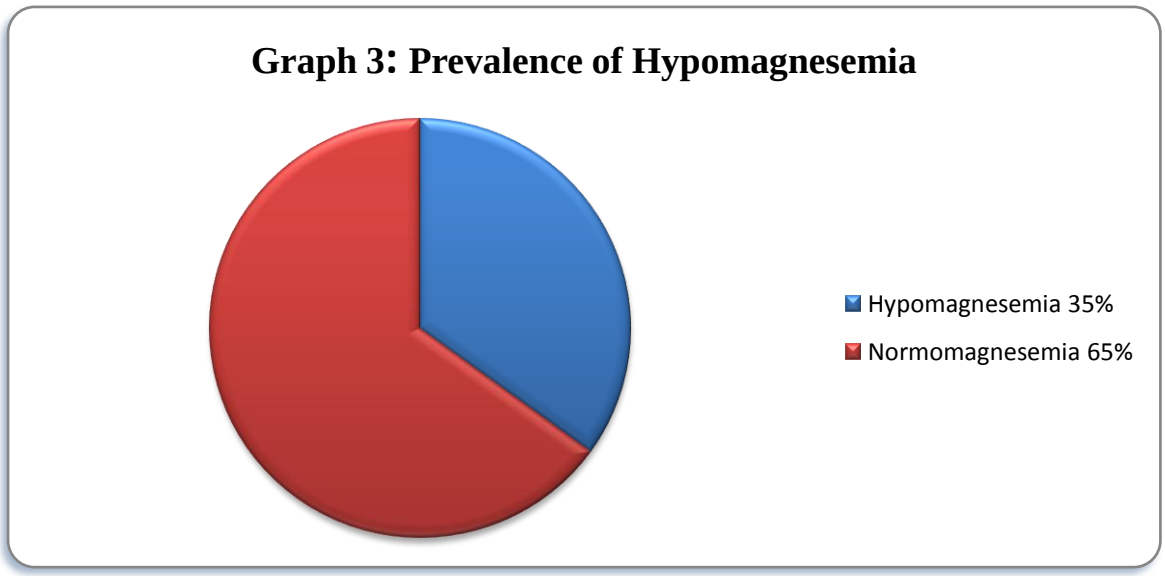
The average duration of diabetes in study population was 8.89 years and range was 2 year to 23 years. 67 patients received only oral hypoglycemic agents and 33 patients received both. 30 patients had hypertension and 15 patients had ischemic heart disease and 55 patients had no comorbidities. Total 35 patients had diabetic retinopathy. Total of 15 patients had diabetic neuropathy. 33 patients had Nephropathy.

Table 3: Prevalence of Hypomagnesemia

Sex	Magnesium		Statistical inference
	Normomagnesemia (n=65)	**Hypomagnesemia (n=35)**	
Male	34 (52.3%)	16 (45.7%)	X^2=.396 Df=1 .529>0.05 Not Significant
Female	31 (47.7%)	19 (54.3%)	

Sl.no	MG	Mean	S.D	Statistical inference
1	Male (n=50)	.4920	.72530	T=-.622 df=98 .536>0.05 Not Significant
2	Female (n=50)	.5840	.75468	



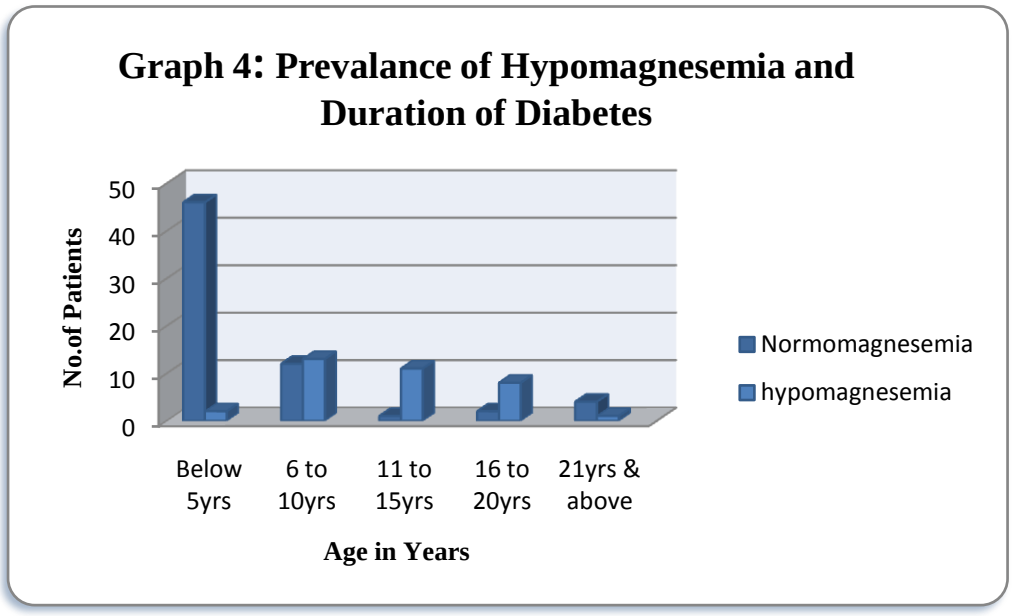
Hypomagnesemia was found in 35 patients. 65 patients had normomagnesemia No patient had hypermagnesemia. No correlation was found between hypomagnesemia in men and women (45.7% and 54.3%% respectively).

Table 4: Prevalence of Hypomagnesemia and duration of diabetes

Oneway ANOVA

Sl.no	MG	Mean	S.D	SS	Df	MS	Statistical inference
1	Between Groups			32.917	4	8.229	F=13.265 .060<0.05 Not Significant
2	Below 5yrs (n=45)	.0000	.00000				
3	6 to 10yrs (n=25)	.8040	.78977				
4	11 to 15yrs (n=15)	1.4333	.40119				
5	16 to 20yrs (n=10)	1.2200	.64601				
6	21yrs & above (n=5)	.0000	.00000				
7	Within Groups			20.979	95	.221	

Sl. no	Duration(years)	Magnesium		Statistical inference
		Normomagnesemia (n=65)	Hypomagnesemia (n=35)	
1	Below 5yrs	46 (70.8%)	2 (5.7%)	X^2=4.568
2	6 to 10yrs	12 (18.5%)	13 (37.1%)	Df=4
3	11 to 15yrs	1 (1.5%)	11 (31.4%)	.067>0.05
4	16 to 20yrs	2 (3.1%)	8 (22.9%)	Not
5	21yrs & above	4 (6.2%)	1 (2.9%)	Significant



chi-square ($\chi 2$) value is 4.568.So the correlation is insignificant p value. So, the duration of diabetes not significantly predict serum magnesium concentration. Oneway ANOVA F=13.265 in between groups also shows no significant correlation. The mean duration was 8.89 years (2-23).

Table 5: Prevalence of Hypomagnesemia and Mode of Diabetic treatment

Treatment mode	Magnesium		Statistical inference
	Normomagnesemia (n=65)	Hypomagnesemia (n=35)	
OHA	45 (69.2%)	22 (62.9%)	X^2=.418 Df=1 .518>0.05 Not Significant
OHA+insulin	20 (30.8%)	13 (37.1%)	

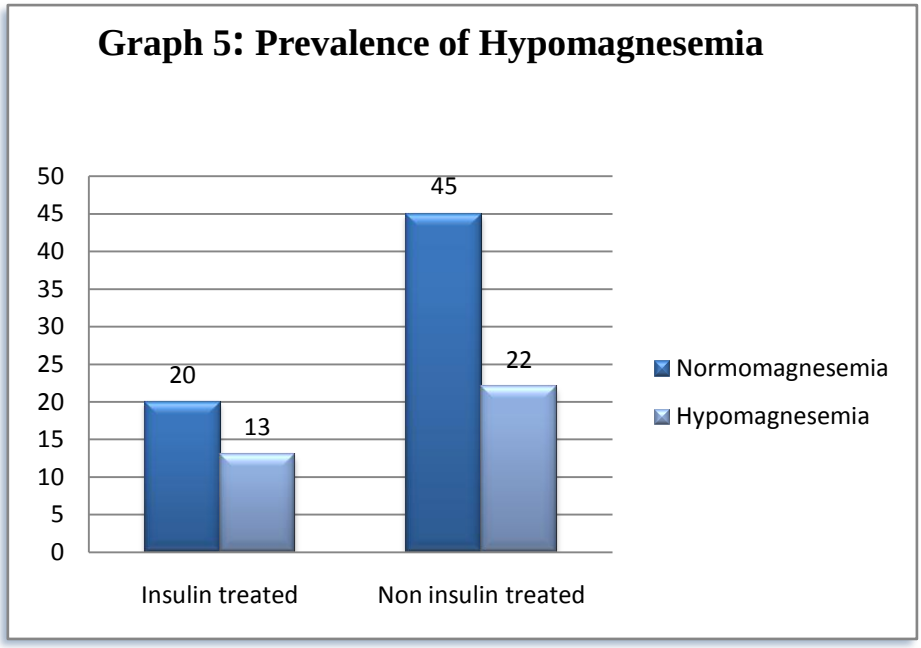
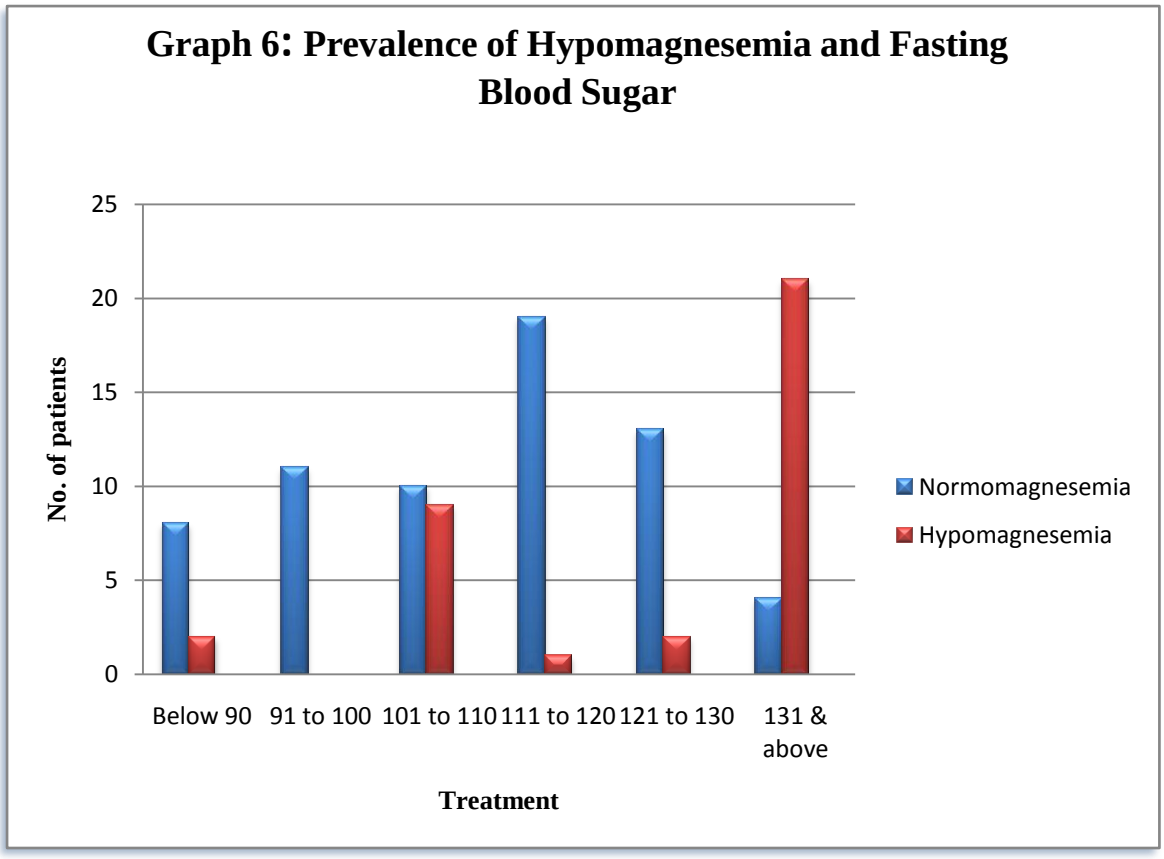


Table 6: Prevalence of Hypomagnesemia and Fasting blood sugar

Sl.No	FBS	Magnesium		Statistical inference
		Normomagnesemia (n=65)	Hypomagnesemia (n=35)	
1	Below 90	8 (12.3%)	2 (5.7%)	X^2=45.582 Df=5 .000<0.05 Significant
2	91 to 100	11 (16.9%)	0	
3	101 to 110	10 (15.4%)	9 (25.7%)	
4	111 to 120	19 (29.2%)	1 (2.9%)	
5	121 to 130	13 (20%)	2 (5.7%)	
6	131 & above	4 (6.2%)	21 (60%)	



Prevalence of hypomagnesemia is high when fasting blood sugar >131(60%). The chi-square ($\chi 2$) value is 45.582. So the correlation is significant. So, fasting blood sugar can significantly predict serum magnesium concentration.

Table 7: Prevalence of Hypomagnesemia and HbA1c

Sl.no	HbA1C	Magnesium		Statistical inference
		Normomagnesemia (n=65)	Hypomagnesemia (n=35)	
1	Below 6	8 (12.3%)	2 (5.7%)	X^2=10.408 Df=5 .064>0.05 Not Significant
2	6 to 7	18 (27.7%)	5 (14.3%)	
3	7 to 8	15 (23.1%)	5 (14.3%)	
4	8 to 9	5 (7.7%)	9 (25.7%)	
5	9 to 10	8 (12.3%)	4 (11.4%)	
6	10 & above	11 (16.9%)	10 (28.6%)	

Serum magnesium concentration showed no significant association with HbA1C. Chi square X^2=10.408,Df=5 P value .064 . Higher prevalance of hypomagnesemia observed in HbA1c > 10 (28.6%).

Graph 7: Prevalence of Hypomagnesemia and HbA1C

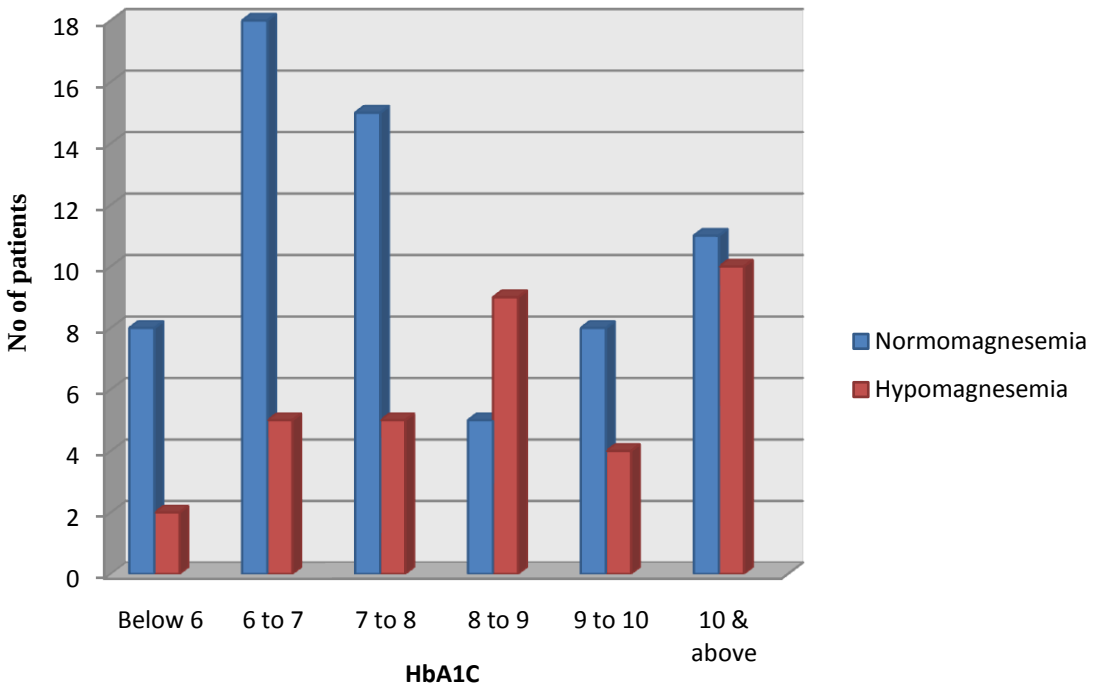


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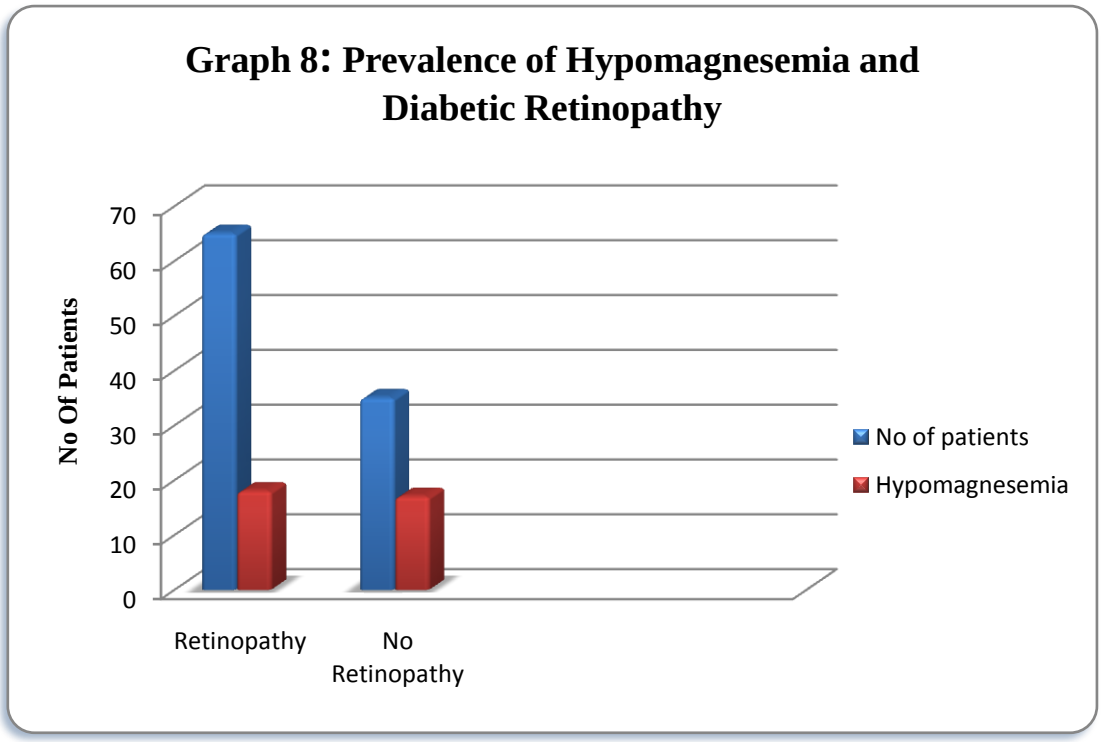
Table 8: Prevalence of Hypomagnesemia and Diabetic Retinopathy

Particulars	No.of Patients (n=100)	Percentage (100%)
No Retinopathy	65	65.0
NPDR	33	33.0
PDR	2	2.0

Sl.no	Retinopathy	Magnesium		Statistical inference
		Normomagnesemia (n=18)	hypomagnesemia (n=17)	
1	NPDR	18 (100%)	15 (88.2%)	X^2=4.746 Df=1 .034<0.05 Significant
2	PDR	0	2 (11.8%)	



Observations revealed a definite correlation between hypomagnesemia and diabetic retinopathy. The chi-square ($\chi 2$) value is 4.746. Df=1 .p value is 0.034.

TABLE.9: Prevalence of Hypomagnesemia and Diabetic Neuropathy

Particulars	No. of patients (n=100)	Percentage (100%)
No neuropathy	85	85.0
neuropathy	15	15.0

Sl.no	Neuropathy	Magnesium		Statistical inference
		Normomagnesemia (n=65)	Hypomagnesemia (n=35)	
1	Negative	60 (92.3%)	25 (71.4%)	X^2=7.778 Df=1 .005<0.05 Significant
2	Positive	5 (7.7%)	10 (28.6%)	

Observations revealed a definite correlation between hypomagnesemia and diabetic neuropathy. The chi-square ($\chi 2$) value is 7.778. Df=1 .p value is 0.005.

Graph 9: Prevalence of Hypomagnesemia and Diabetic Neuropathy

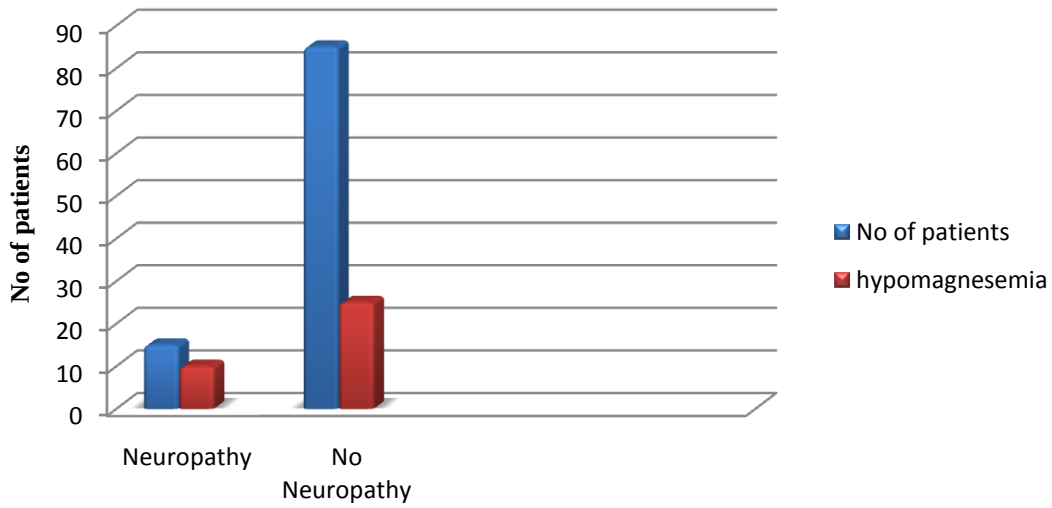
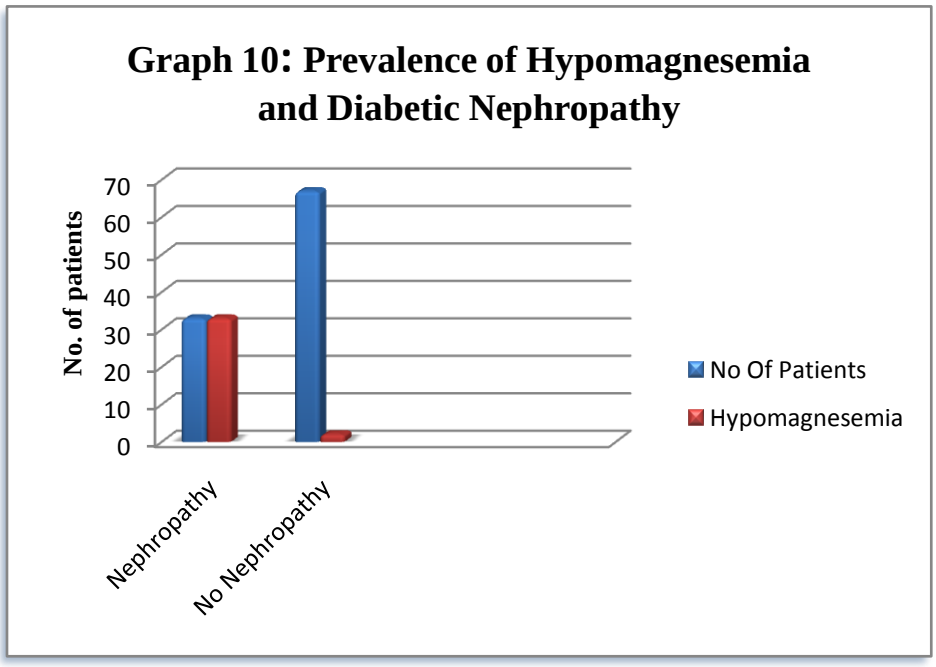


Table 10: Prevalence of Hypomagnesemia and Diabetic Nephropathy

Particulars	No.of persons (n=100)	Percentage (100%)
No albumminuria	67	67.0
Macroalbuminuria	4	4.0
Microalbuminuria	29	29.0

Sl. no	Nephropathy	Magnesium		Statistical inference
		Normomagnesemia (n=65)	Hypomagnesemia (n=35)	
1	No albuminuria	65 (100%)	2 (5.7%)	X^2=91.471 Df=2 .000<0.05 Significant
2	Macroalbuminuria	0	4 (11.4%)	
3	Microalbuminuria	0	29 (82.9%)	



Observations revealed a definite correlation between hypomagnesemia and diabetic nephropathy. The chi-square ($\chi 2$) value is 91.471. Df=2 .

Table 11: Prevalence of Hypomagnesemia and Ischemic Heart Disease

Sl.no	IHD	Magnesium		Statistical inference
		Normomagnesemia (n=65)	Hypomagnesemia (n=35)	
1	Absent	54 (83.1%)	31 (88.6%)	X^2=.539 Df=1 .463>0.05 Not Significant
2	Present	11 (16.9%)	4 (11.4%)	

Serum magnesium concentration showed no significant relation with ischemic heart disease, X^2=.539,Df=1.P value is insignificant.

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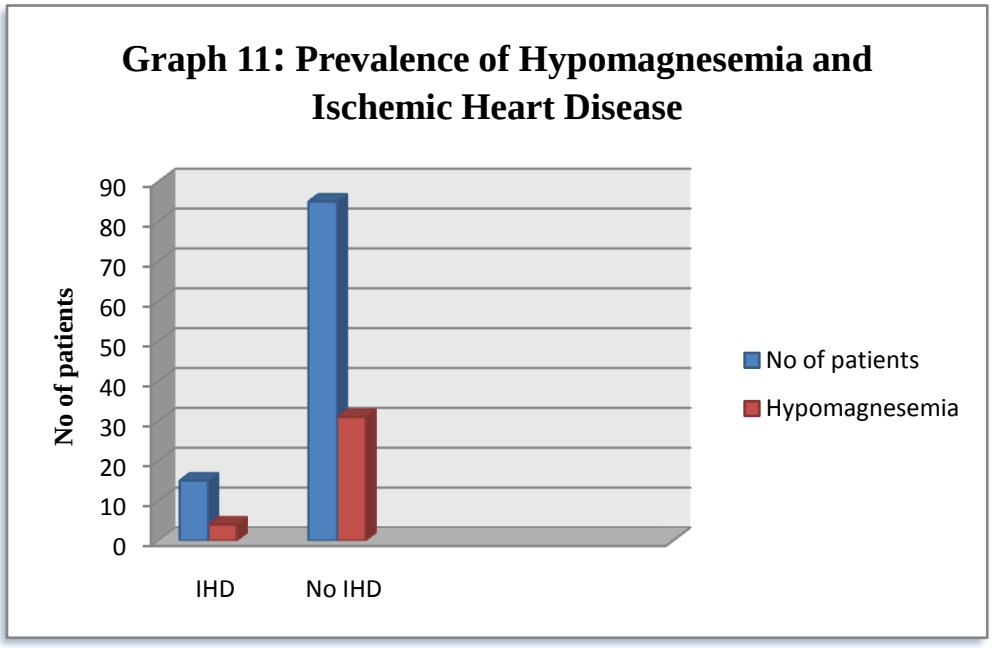

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Table 12: Prevalence of Hypomagnesemia and Hypertension

Sl.no	SHT	Magnesium		Statistical inference
		Normomagnesemia (n=65)	Hypomagnesemia (n=35)	
1	Absent	43 (66.2%)	27 (77.1%)	X^2=1.308 Df=1 .253>0.05 Not Significant
2	Present	22 (33.8%)	8 (22.9%)	

Serum magnesium concentration showed no significant with systemic hypertension, X^2=1.308,Df=1.P value is insignificant

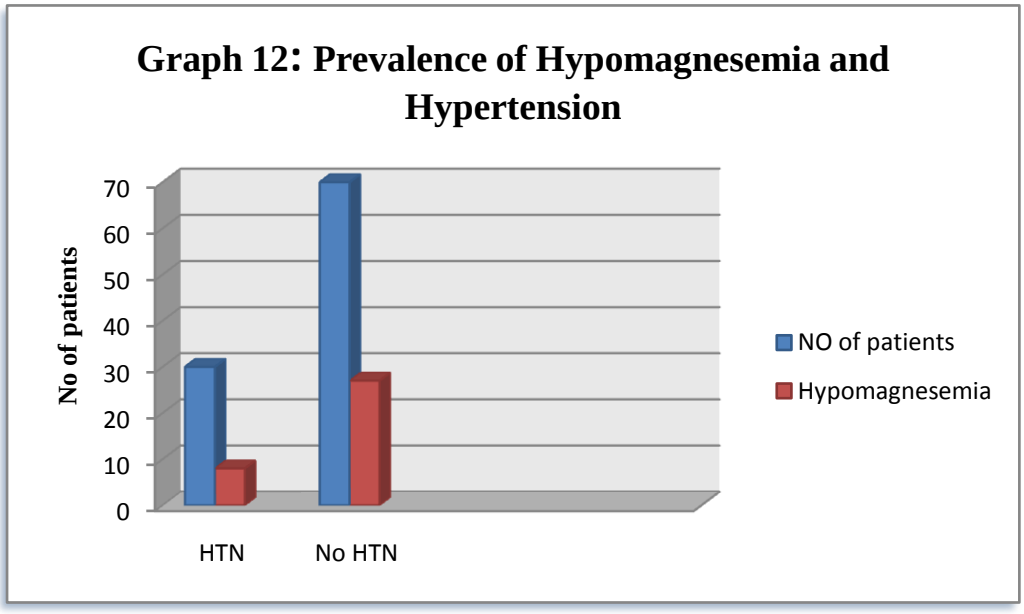

Table 13: Distribution of Complications

COMPLICATIONS	**Hypomagnesemia** (no=35)	**Normomagnesemia** (no=65)
IHD	4(11.4%)	11(16.9%)
HTN	8(22.9%)	22(33.8%)
RETINOPATHY	35(48.6%)	18(27.7%)
NEUROPATHY	10(28.6%)	5(7.7%)
NEPHROPATHY	33(94.3%)	0
FBS 131 & ABOVE	21(60%)	4(6.2%)

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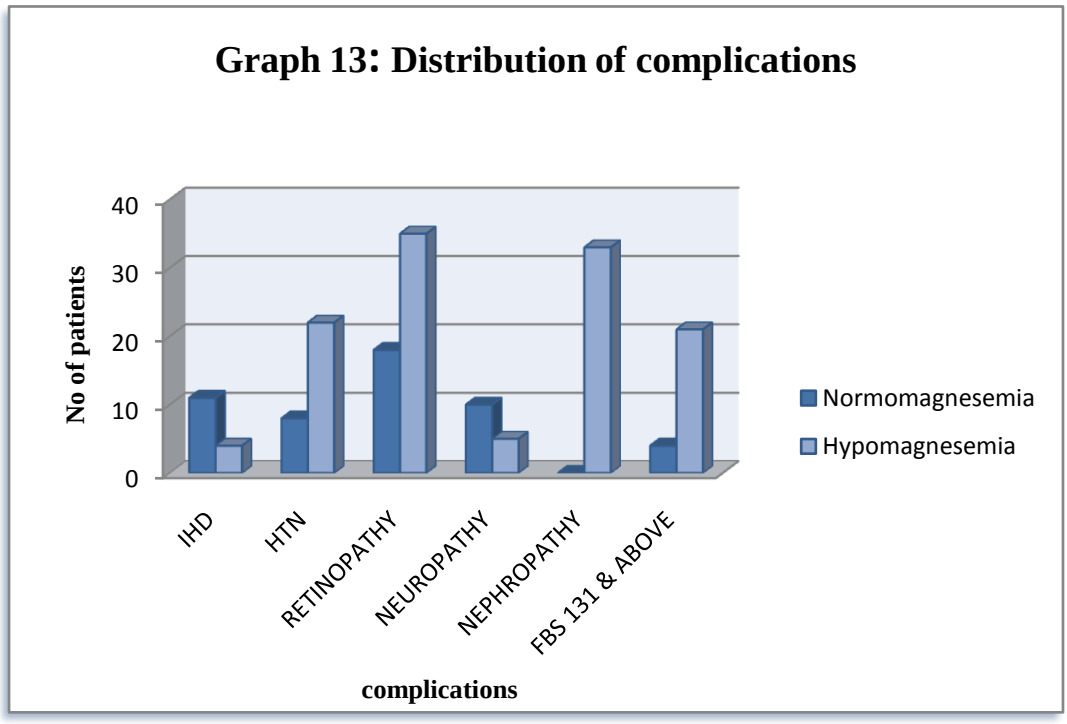

Among the persons with low serum magneseum level prevalence rates of IHD , HTN, Diabetic neuropathy, Diabetic nephropathy,Diabetic Retinopathy and Fasting glucose levels were compared to normomagnesemic group. Study shows increased incidence of Diabetic neuropathy, Diabetic nephropathy, Diabetic Retinopathy in hypomagnesemic patients compared to normomagnesemics.

DISCUSSION

Reports of increase prevalence of low plasma magnesium concentrations among diabetic patients and possible association of hypomagnesemia with diabetic complications prompted this study.

Marked magnesium deficiency has been reported in the previous case series of type-2 DM. However, some workers have also reported normal and even high levels.[58] The present study, shows serum magnesium level of 35 cases with type 2 DM, below the reference range. This confirms to the reported prevalence of low plasma magnesium status in T2DM in several studies, which ranged from 13.5% to 47.7%. Prevalence of hypomagnesemia in T2 DM in our study was similar to that reported by Nadler et al.[56] Walti MK et al.[60] also reported a 37.6% prevalence of hypomagnesemia in T2DM versus 10.9% in nondiabetic controls in Zurich, Switzerland.

Serum magnesium concentration though less sensitive, is a highly specific indicator of low magnesium status.

Low dietary intake is an unlikely cause of impaired magnesium status in diabetes. A dietary assessment conducted in Europe showed that only 5.4 percentage of the diabetics and 9.1perccentage of the control group had magnesium intake less than reference range . In addition, recently it has been shown that controlled diabetics have absorption of magnesium to a similar as

healthy controls. Increased urinary magnesium excretion due to hyperglycemia and osmotic diuresis may contribute to hypomagnesemia in diabetes.

Serum levels of magnesium have been found by several investigators to correlate inversely with fasting blood glucose concentration and the percentage of HbA1C. Schlienger et al.[59] hypothesized that patients with uncontrolled diabetics showed low serum magnesium concentration. The present study also revealed statistically significant correlation between serum magnesium levels and fasting blood sugar (Prevalence of hypomagnesemia high in fasting blood sugar value above 131 mgs% is 60%) but there is no significant correlation with HbA1C. However a higher prevalance of hypomagnesemia is observed in HbA1c > 10 (28.6%) in the present study.

Hypomagnesemia is reported to be both a cause and result of poor glycemic control. Magnesium is necessary for glucose entry into the cell and act as a cofactor for enzymes of carbohydrate metabolism. In addition, magnesium deficiency has been shown to promote insulin resistance in multiple studies. Nadler et al.[56] have reported that insulin sensitivity decreases even in nondiabetics individuals after induction of magnesium deficiency. Likewise, elderly subjects were shown to have improved glucose tolerance when they received magnesium supplements. Thus hypomagnesemia by itself results in poor glycemic control.

Conversely, hyperglycemia and osmotic diuresis may lead to increased urinary magnesium excretion and hypomagnesemia in diabetics. However, high prevalence of hypomagnesemia is reported in type – 2 diabetics with good glycemic control. So, although poor glycemic control is associated with magnesium deficiency, it is not simply induced by hyperglycemia and is not corrected by improvement in metabolic control alone.

Sex, age duration of diabetes were not the significant predictors of serum magnesium levels. Yajnick et al.[58] in 1984 reported that among patients with DM serum magnesium levels depends on age and males had higher serum magnesium levels than females. The increasing magnesium levels with age were probably due to impaired renal function and the sample size, (87 diabetics, 30 non diabetics) was relatively small to confirm male preponderance. In our study, patients with impaired renal functions were excluded. Our results confirm to the recent reports that have not shown any significant associations between sex, age and duration of diabetes with serum magnesium levels.[61]

Significant differences, in serum magnesium concentrations have been reported between the insulin treated and non-insulin treated diabetics. In our study revealed prevalence of hypomagnesemia is low in insulin treated patients compared to non insulin treated patients. ((37.1% v/s 62.9%) . Yajnik et al.[58] reported that insulin treated diabetics have significantly lower serum magnesium levels compared to non insulin treated ones. However, the

difference was statistically not significant. Walti MK et al[61] have reported that diabetes treatment (insulin or OHA) did not significantly predict hypomagnesemia. Insulin mediates entry of magnesium from plasma to RBC. In a recent study Alzaida et al.[50] have found that cellular uptake of magnesium is normally stimulated by insulin. So insulin treatment may enhance cellular magnesium uptake and result in increased prevalence of hypomagnesemia.

In our study, no association was found between incidence of ischemic heart disease and hypomagnesemia. However, several observational studies have reported hypomagnesemia is associated with higher risk of ischemic heart disease. As part of Atherosclerosis risk in communities study, a cohort of 15,792 subjects were studied over 7 years and an increasing relative risk of coronary artery disease with decreasing serum magnesium was reported.[39] How a low serum magnesium predisposes to coronary artery diseases is not identified yet. However, in our study, no difference in prevalence of hypomagnesemia was found between those with ischemic heart disease and others. Similarly, no difference in prevalence of hypomagnesemia was found between the hypertensive and non hypertensive subjects.

Trails have shown that magnesium deficiency has been associated with diabetic microvascular disease. In our study increased prevalence of hypomagnesemia was observed in diabetics with microvascular complications

and mean serum concentration of magnesium in diabetics with microvascular complications was comparatively lower than in diabetics with no microvascular complications.

Hypomagnesemia has been reported in patients with diabetic retinopathy, with lower magnesium levels predicting a greater risk of severe diabetic retinopathy. Our observations revealed a definite association between diabetic retinopathy and lower serum magnesium levels. There was a significant difference is prevalence of hypomagnesemia in diabetics with retinopathy and without retinopathy (48.6% Vs 27.7%; P< 0.005). These observations are similar to other reports. Grafton et al.[57] have proposed the inositol transport theory to explain this association. But the exact reason remains obscure.

Hypomagnesemia is seen in cases with diabetic neuropathy, with lower magnesium levels predicting a greater risk of severe diabetic neuropathy. The present study revealed patients with diabetic neuropathy had a slightly higher prevalence of hypomagnesemia compared to those without neuropathy (28.6% v/s 7.7%). Rodriguez- Moran and Guerrero-Romero hypothesized that low serum magnesium level causes high incidence of diabetic foot ulcers. .

Hypomagnesemia is seen in cases with diabetic nephropathy. Decreased magnesium levels predicts a increased risk of severe diabetic nephropathy. The present study shows patients with diabetic nephropathy had a slightly increased incidence of hypomagnesemia than in those without nephropathy(94.3% v/s

0%). Corsonello, et al demonstrated decreased serum magnesium in type 2DM with nephropathy compared to normal patients. Recent study, shows that decreased magnesium concentration is associated with rapid loss of renal function in patients with type 2DM.

In summary, the present study has demonstrated that hypomagnesemia is common in type2 diabetics and magnesium deficiency is conclusively associated with diabetic retinopathy, neuropathy, nephropathy.

Diabetic patients need regular monitoring of serum magnesium concentration. If low level is reported magnesium supplementation is necessary.

CONCLUSION

1) Prevalence of hypomagnesemia in type2 Diabetics is 35%.

2) Prevalence of hypomagnesemia is higher in Patients with microvascular diabetic complications than in those without microvascular complications.

3) Hypomagnesemia is significantly associated with retinopathy, neuropathy and nephropathy.

4) No significant association was seen with ischemic heart disease and Hypomagnesemia.

5) No significant association was seen with Hypertension and Hypomagnesemia.

6) Prevalence of hypomagnesemia was high in patients with fasting blood sugar >131mg/dl.

7) No significant differences were seen among both sexes.

8) No significant association of hypomagnesemia were seen with duration of diabetes and HbA1c levels.

SUMMARY

Present study was conducted to estimate the prevalence of hypomagnesaemia in type 2 diabetics and to study the possible association of hypomagnesaemia with diabetic complications and comorbidities.

The study included 100 type 2 diabetic cases, with no factors significantly altering the serum magnesium levels. Fasting serum magnesium levels were estimated and correlation was done with variable parameters.

The results found that prevalence of low magnesium levels(<1.7 mg/dl) in type 2 diabetic cases were 35% and magnesium deficiency was significantly associated with diabetic retinopathy, neuropathy and nephropathy . No significant correlation was identified with other parameters – IHD, hypertension, duration of diabetes and treatment modality. Causes of hypomagnesemia are multifactorial. Because available data suggests that low magnesium levels associated with adverse clinical outcomes. So it is prudent in clinical practice to periodically monitor plasma magnesium concentrations in diabetic patients and the condition corrected whenever possible.

BIBLIOGRAPHY

1.Wild S, Roiglic G, Grren A, Sicree R, King H. Global Prevalence of Diabetes. Diabetes Care, 2009, 27:1047–1053.

2.Nicki R.Colledge,Brian R.Walker, Stuart H.Raiston; Davidson' Principles & practice of medicine 21st Edition P 795-834.

3. Ramachandran A, Mary S, Yamuna A, Murugesan N, Snehalatha C: High Prevalence of Diabetes and Cardiovascular Risk Factors Associated with urbanization in India: Diabetes Care, 2008, 31:893–898.

4.Riduara RL,Stamfer MJ,Willet WC,et al.Magnesium intake and risk of type 2 diabetes mellitus in men and women .Diabetes care 2004:27:134-140

5.Huerta MG, Holmes V F, Romenich J N ,et al .magnesium deficiency is associated with insulin resistance in obese children. Diabetes care 2005:28:1175-1181.

6.Yajnik CS ,smith RF ,Hockaday TD, Ward NI.Fasting plasma magnesium concentration and glucose disposal in diabetes BMJ 1984: 288:1032-1034

7. Hatwal A,Gujral AS,Bhatia RP, Agarwal JK,Bajpai HS.association of hypomagnesemia with diabetic retinopathy Acta Ophthalmol 1989:67:714-716.

8.Sasaki S, Oshima T ,Matsuura H,et al .Abnormal magnesium status in patients with cardiovascular disease Clin sci(Colch). 2000; 175-181

9. Paolisso G, Passariello N, Pizza G ,et al. Dietary magnesium replacement B cell response to glucose and arginine in elderly non insulin dependent diabetic subjects .Acta endocrinol 1989;121:16-20

10. Von MJ, Minowski O, Diabetes Mellitus and pancreas extirpation. Arch. Exper. Path Pharm. 1980; 26: 371-87.

11. Carpenter MW, Coustan OR. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol. 1982; 144: 768-73.

12. Aiello LP. Diabetic retinopathy (Technical Review). Diabetes Care. 1998; 21: 143-56.

13. UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998: 352: 854-65.

14. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). BMJ. 1998; 317; 708-13.

15. Pickup J., Williams G. Text book of Diabetes: Clinical features of diabetic neuropathy. 2nd Ed. Oxford: Black Well Science; 1997.

16. Widdowson EM, McCance RA, Spray CM. Chemical composition of human body. Clin Sc. 1951; 10: 113-25.

17. Bringhurst FR, Demay MB, Krane SM, Kronenberg HM. Harrison's Principles of Internal Medicine: Magnesium metabolism. 18th Ed. New Delhi: Mc Graw Hill Medical Publishing Division.

18. Dove WF, Davidson N. Cation effects on denaturation of DNA. J Molec Biol. 1962; 5: 467-78.

19. Venner H, Zimmer C. Studies on nucleic acids – changes in stability of DNA secondary structure by interaction with divalent metal ions. Biopolymers 1966; 4:321-35.

20. Edelman IS, Ts'o POP, Vinograd J. Binding of magnesium to microsomal nucleoprotein and ribonucleic acid. Biochem et biophys acta. 1960; 43: 393-403.

21. Haenni A, Ohrvall M, Lithell H. Magnesium homeostasis. Metabolism. 2001; 50:1147-51.

22. US Department of Agriculture. Agricultural Research Service: USDA National Nutrient Database for standard reference, Release 16, 2003: Nutrient Data Laboratory Home Page http://www.nal.usda.gov/fnic/food comp.

23. Whang R, Oei JO. Predictors of clinical hypomagnesemia. Arch Intern Med. 1984; 144: 1794 – 96.

24. Swales JD. Magnesium deficiency and diuretics. BMJ. 1982; 285: 1377-8.

25. Wong ET, Rude RK, Singer FR. A high prevalence of hypomagnesemia in hospitalized patients. Am J Clin Pathol. 1983; 79: 348-52.

26. Chernow B, Bamberger S, Stoiko M. Hypomagnesemia in patients in postoperative intensive care. Chest. 1989; 95: 391-97.

27. Whang R, Ryder KW. Frequency of hypomagnesemia and hypermagnesemia-Requested versus routine. JAMA. 1990; 263: 3063-4.

28. Monico EP, Bachman D, Anthony RG. Hypomagnesemia. Am J Emerg Med. 1997; 15(4): 441-2.

29. Vallee B, Wacker WE, Ulmer DD. The magnesium deficiency tetany syndrome in man. N Engl J Med. 1960; 262: 155-61.

30. Tsuzi H, Venditti FJ Jr., Evans JC. The associations of levels of serum potassium and magnesium with ventricular premature complexes. The Framingham Heart Study. Am J cardiol. 1994; 74: 232-35.

31.Zipes DP. Braunwald's Heart Disease - A Textbook of Cardiovascular Medicine: Specific arrhythmias – Diagnosis and treatment. 7th Ed. Philadelphia: Saunders; 2005.

32. Dyckner T. Serum magnesium in acute myocardial infarction – Relation to arrhythmias. Acta Med Scand. 1980; 207: 59-66.

33. Kafka H. Langevin L. Armstrong PW. Serum magnesium and potassium in acute myocardial infarction. Arch Intern Med. 1987; 147: 465-69.

34. Grillo JA. Gonzalez ER. Changes in pharmacotherapy of CPR. Heart Lung. 1993; 22: 548-53.

35. Yamori Y, Nara Y, Mizushima S. Nutritional factors for stroke and major cardiovascular diseases – International Epidemiological Comparison of Dietary Prevention. Health Rep. 1994; 6(1): 22-7.

36. Ascherio A, Rimm EB, Giovannucci EL, Coldifz GA, Rosner B, Willett WC, et al. A prospective study of nutritional factors and hypertension among US men. Circulation 1992; 86: 1475-84.

37. National Heart, Lung and Blood Institute. Joint National Committee for Prevention, Detection, Evaluation and Treatment of high blood pressure-The sixth report. Arch Intern Med 1997; 157: 2413-46.

38. Dyckner T, Wester PO. Effect of magnesium on blood pressure. BMJ. 1983; 286: 1847-49.

39. Liao F, Folsom AR, Brancati FL. Is low magnesium concentration a risk factor for coronary heart disease? The ARIC study. Am Heart J. 1998; 136: 480-90.

40. Ford ES. Serum magnesium and ischemic heart disease – Findings from a national sample of US adults. Intl J of Epidem. 1999; 28: 645-51.

41. Babel S, Bhatnagar NS, Bhatnagar LK. Serum magnesium levels in acute myocardial infarction and its prognostic significance. JAPI. 1983; 31: 12-4.

42. Ascherio A, Rimm EB, Hernan MA, Giovannucci EL, Kawachi J Stampfer MJ. Intake of potassium, magnesium, calcium and fibre and risk of stroke among US men. Circulation. 1998; 98: 1198-204.

43. Rude RK, Olerich M. Magnesium deficiency – Possible role in osteoporosis. Osteoporos Int. 1996; 6: 453-61.

44. Lal J, Vasudev K, Kela AK, Jain SK. Effect of oral magnesium supplementation on lipid profile and blood glucose of patients with type 2 diabetes mellitus. JAPI. 2003; 51: 37-42.

45. Nadler JC, Malayan S, Luong H, Shaw S, Natarajan R, Rude RK. Intracellular free magnesium deficiency plays a key role in increased platelet reactivity in type 2 diabetes mellitus. Diabetes care 1992; 15: 835-41.

46. Dzurik R, Stetikova K, Spustova V. The role of magnesium deficiency in insulin resistance- an invitro study. J Hypertens 1991; 9(6): S312-3.

47. Reaven GM. Role of insulin resistance in human disease. Diabetes 1988; 37: 1575–607.

48. Garland HO. New experimental data on the relationship between diabetes mellitus and magnesium. Magnes Res. 1992; 5: 193-202.

49. Durlach J, Altura B, Altura BM. Highlights and summary of the 10th Annual French Colloquium on magnesium. Magnesium 1983; 2: 330-6.

50. Alzaida A, Dinneen SF, Moyer TP, Rizza RA. Effects of insulin on plasma magnesium in noninsulin dependant diabetes mellitus – evidence for insulin ressitance. J Clin Endocrinol Metab. 1995; 80: 1376-81.

51. Paolisso G, Sgambato S. Daily magnesium supplements improve glucose handling in elderly subjects. Am J Clin Nutr. 1992; 55: 1161-7.

52. Paolisso G, DeRiu S. Impaired insulin mediated erythrocyte magnesium accumulation in nondiabetic obese patients. Diabetes metab. 1990: 16: 328-33.

53. Tonyai S, Motto C. Erythrocyte membrane in magnesium deficiency. Am J Nutr. 1985: 4: 399.

54. Tosiello L. Hypomagnesemia and Diabetes mellitus: A review of clinical implications. Arch. Intem. Med. 1996; 156: 1143-8.

55. Eichhorn EJ, Tandon PK, DiBianco R. Clinical and prognostic significance of serum magnesium concentration in patients with severe chronic congestive heart failure. The PROMISE study. J Am Coll Cardiol. 1993; 21: 634-40.

56. Nadler JL, Buchnan T, Natarajan R, Antonipillai I, Bergman R, Rude RK. Magnesium deficiency produces insulin resistance and increased thromboxane synthesis. Hypertension. 1993; 21: 1024-9.

57.Grafton G, Baxter MA, Sheppard MC. Effects of magnesium on sodium dependant inositol transport. Diabetes. 1992; 41: 35-9.

58. Yajnick CS, Smith RF, Hockaday TDR, Ward NI. Fasting plasma magnesium concentration and glucose disposal in diabetes. BMJ 1984; 288: 1032-4.

59.Schlinger JL, Grunenberger F, Maier EA, Simon C, Chabrier G, Leroy MJF. Disturbances of plasma trace elements in diabetes – relations with glycemic control. Presse Med. 1988; 17: 1076-9.

60.Walti MK, Zimmermann MB, Hurrell RF. Low plasma magnesium in type-2 diabetes. Swiss Med Wkly. 2003; 133: 289-92.

61.Walti MK, Zimmermann MB, Hurrell RF. Low plasma magnesium in type-2 diabetes. Swiss Med Wkly. 2003; 133: 289-92.

ANNEXURE I- ABBREVIATIONS

T1 and T2DM	─Typy1 and type2 Diabetes Mellitus
HTN	─ Systemic Hypertension
CAD/IHD	─ Coronary Artery Disease/ Ischemic Heart Disease
CVA	─ Cerebrovascular Disease
FPG/FBS	─ Fasting Plasma Glucose/ fasting blood sugar
PPPG/PPBS	─ Post Prandial Plasma Glucose/ Post Prandial Blood sugar.
HDL	─ High Density Lipoprotein
VLDL	─Very low Density Lipoprotein
ECG	─ Electrocardiogram
IGT	─ Impaired Glucose Tolerance
HbA1C	─ Glycosylated Haemoglobin
IFG	─ Impaired Fasting Glucose
OGTT	─ Oral Glucose Tolerance Test

ANNEXURE II – PROFORMA

Serial No. :

Patient Details

Name :

Hospital No. :

Age :

Sex :

Occupation :

Diabetic History

Age of onset :

Total Duration :

Mode of Treatment

1. Oral hypoglycemic agents :

2. Insulin (Type) :

3. Diabetic Diet :

Symptoms Related to Complications

A) Symptoms of Neuropathy

- Postural dizziness :
- Weakness :
- Numbness/parasthesia :
- Pain/hyperaesthesia :

• Bladder incontinence :

• Impotence :

B) Symptoms of Nephropathy

• Oliguria :

• Oedema :

C) Symptoms of Retinopathy

• Dimness of vision :

• Blindness :

Past History

• IHD : • HTN :

Family History

• DM :

• IHD :

• HTN :

Examination

Height : Weight :

General Examination:

Pulse Rate: Icterus : Cyanosis: Clubbing: Lymph Nodes:

Edema:

BP: Supine: Standing:

A. Sensory motor Neuropathy

• Loss of pain and temperature sense :

• Loss of touch :

• Loss of position and vibration sense :

• Rhomberg test :

B. Proximal Muscle Neuropathy

• Wasting :

• Power :

• Tone :

• Knee jerk :

• Ankle jerk :

C. Eye Signs

• Diabetic retinopathy :

- Non Proliferative :
- Proliferative :

D. Signs of nephropathy

• Oedema :

• Facial puffiness :

E. Cardiovascular system

F. Respiratory system

G. Abdomen

Investigations

1. FBS: PPBS: HbA1C :

2. Serum Magnesium:

3. 24 hour albuminuria:

4. Urea: Creatinine:

5. Routine Urine:

Sugar: Protein : Microscopy:

6 ECG:

7 Nerve conduction study:

ANNEXURE III-MASTER CHART

S.NO	NAME	HOSPITAL NO	AGE	SEX	AGE OF ONSET	S)	TREATMENT MODE	IHD	SHT	RETINOPATHY	NEUROPATHY	NEPHROPATHY	FBS	PPBS	HbA1C	Mg
1	Sundarraj	2153	50	m	46	4	oha	A	A	A	A	A	90	130	5.8	2
2	Balasubramanian	2168	58	m	48	10	oha+insulin	A	A	NPDR	A	Microalbuminuria	102	145	6.6	1.5
3	Rajendran	2169	56	m	46	10	oha+insulin	A	P	NPDR	P	Microalbuminuria	155	160	11.1	1.6
4	Jothiraman	2175	65	m	53	12	oha	A	P	pdr	A	Microalbuminuria	120	180	8	1.5
5	Rajamanikam	2201	65	m	54	11	oha	P	P	NPDR	P	Microalbuminuria	105	145	5.4	1.4
6	Samivel	2198	60	m	56	14	oha+insulin	A	P	NPDR	P	Microalbuminuria	145	166	7.8	1.6
7	Sekar	2196	55	m	45	10	oha	A	A	NPDR	A	Microalbuminuria	102	170	9.6	1.5
8	Govindaraj	2211	78	m	56	22	oha+insulin	A	A	NPDR	P	A	112	184	8.8	2.1
9	Singaram	2214	75	m	54	21	oha	A	A	A	P	A	120	175	5.8	2.2
10	Ramalingam	2217	62	m	48	14	oha	A	A	A	P	Microalbuminuria	155	196	6.6	1.6
11	Devendran	26234	42	m	40	2	oha	A	A	A	A	A	100	185	8.5	2.4
12	Johnson	26239	45	m	42	3	oha	A	A	A	A	A	80	130	6.8	2.2
13	Kandasamy	2756	78	m	56	22	oha+insulin	P	P	NPDR	P	A	120	155	9.8	2.1
14	Visvalingam	2757	53	m	49	4	oha	A	A	A	A	A	102	154	8.6	2.4
15	Selvaraj	2750	57	m	47	10	oha+insulin	A	A	NPDR	A	Microalbuminuria	145	190	5.4	1.6
16	Pandiyan	2754	70	m	52	18	oha+insulin	P	P	NPDR	A	A	112	165	10.6	2.2
17	Ravi	2357	45	m	41	4	oha	A	A	A	A	A	100	155	6.8	2.1
18	Mahalingam	2359	55	m	51	4	oha	A	A	A	A	A	140	200	9.8	2.2
19	Narayanasamy	2461	63	m	53	10	oha	A	A	pdr	A	Microalbuminuria	106	170	8.5	1.5
20	Ramasamy	2462	45	m	42	3	oha	A	A	A	A	A	112	146	10.5	2.2
21	Subramanyam	2463	51	m	47	4	oha	A	A	A	A	A	80	130	5.4	2.4
22	Paulraj	2468	50	m	45	5	oha+insulin	A	P	A	A	A	102	172	7.8	2.4
23	Ayyamperumal	2470	45	m	42	3	oha	A	A	A	A	A	90	165	5.5	2.2
24	Kalilahamed	2472	51	m	48	3	oha	A	P	A	A	A	120	188	7.6	2.4
25	Sekar	2664	50	m	46	4	oha	A	P	A	A	A	95	165	6.4	2.4
26	murugesan	2665	50	m	48	2	oha	A	A	A	A	A	122	174	10.4	2.2
27	mahalingam	2668	65	m	51	14	oha+insulin	A	A	A	P	Microalbuminuria	106	166	7.6	1.6
28	srinivasan	2659	45	m	40	5	oha+insulin	A	A	A	A	A	122	200	10.8	2.4
29	valathan	2892	50	m	46	4	oha	A	P	A	A	A	96	160	6.5	2.4
30	ramalingam	2894	60	m	46	14	oha	A	A	A	A	A	160	200	9.6	1.5
31	mahalingam	2888	42	m	40	2	oha	A	A	A	A	A	112	180	6.4	2.3
32	thangaraj	2885	71	m	53	18	oha	A	A	A	A	Microalbuminuria	140	186	8.5	1.6
33	jayamani	2877	55	m	45	10	oha+insulin	A	A	NPDR	A	A	122	202	11	2.3
34	dachianamoorthi	2881	50	m	47	3	oha	A	A	A	A	A	102	160	6.4	2.3
35	manivel	2878	55	m	46	9	oha	P	P	NPDR	A	A	118	146	7.4	2.4
36	nagarajan	2921	70	m	52	18	oha	A	A	NPDR	A	Microalbuminuria	90	166	8.8	1.5
37	natarajan	2911	65	m	51	14	oha+insulin	A	A	A	A	Microalbuminuria	152	190	9.4	1.5
38	kumarasamy	2919	55	m	50	5	oha	A	A	A	A	A	110	164	9.4	2.4
39	nagarajan	2910	57	m	48	9	oha	P	P	NPDR	A	A	122	153	6.4	2.2
40	saminathan	2912	50	m	47	3	oha	A	A	A	A	A	115	142	7.6	2.2
41	subramanyam	2840	60	m	45	15	oha+insulin	A	A	NPDR	A	Microalbuminuria	140	204	6.6	1.6
42	murugesan	2317	48	m	46	2	oha	A	A	A	A	A	112	174	10.8	2.2
43	narayanan	2320	65	m	55	10	oha+insulin	A	P	A	A	A	122	190	6.8	2.4
44	ponnaiyapillai	2321	51	m	46	4	oha	A	P	A	A	A	105	168	7.6	2.4
45	sarangabani	2327	60	m	45	15	oha	A	A	A	A	A	150	190	9.8	1.5
46	govindan	2500	78	m	56	22	oha+insulin	A	A	NPDR	A	A	115	155	11.4	2.3
47	govindaraj	4084	70	m	54	16	oha+insulin	A	A	NPDR	A	A	136	162	6.4	2.3
48	gunasekaran	4730	48	m	45	3	oha	A	A	A	A	A	105	156	11.1	2.4
49	devendaran	3993	42	m	40	2	oha	A	P	A	A	A	118	146	7.5	2.2
50	sundarraj	2347	52	m	47	5	oha	A	A	A	A	A	80	155	5.4	2.3

S.NO	NAME	HOSPITAL NO	AGE	SEX	AGE OF ONSET	DURATION(YEARS)	TREATMENT MODE	IHD	SHT	RETINOPATHY	NEUROPATHY	NEPHROPATHY	FBS	PPBS	HbA1C	Mg
51	banumathi	2156	52	f	49	3	oha	A	A	A	A	A	126	170	7.6	2.2
52	vijayanthimala	2163	45	f	43	2	oha	A	A	A	A	A	95	130	6.8	2.4
53	neelavathi	2165	60	f	51	9	oha+insulin	P	P	NPDR	A	A	126	176	5.6	2.4
54	mariammal	2166	55	f	46	9	oha+insulin	A	A	NPDR	A	A	110	146	7.4	2.4
55	pitchaiammal	2173	60	f	46	14	oha+insulin	A	A	A	A	Microalbuminuria	140	190	8.4	1.5
56	rengammal	2184	50	f	46	4	oha	A	A	A	A	A	155	174	6.8	2.3
57	mariammal	2185	60	f	46	14	oha	A	A	A	A	Microalbuminuria	90	145	10.6	1.6
58	ramamirtham	2190	61	f	46	15	oha	P	P	NPDR	A	A	130	180	6.6	2.3
59	visalatchi	2219	64	f	49	15	oha+insulin	A	A	NPDR	A	Microalbuminuria	155	210	10.4	1.6
60	panchavarnam	2230	65	f	50	15	oha	A	A	NPDR	A	Macroalbuminuria	126	186	7.4	1.5
61	muthulakshmi	2238	55	f	47	8	oha+insulin	P	P	NPDR	A	A	105	146	9.5	2.3
62	jayashanthi	2240	48	f	45	3	oha	A	A	A	A	A	130	174	11	2.4
63	anjalai	2262	55	f	50	5	oha	A	A	A	A	A	115	146	6.2	2.2
64	sundaravadhini	2263	52	f	48	4	oha	A	A	A	A	A	95	156	10.5	2.4
65	rathinammal	2278	60	f	51	9	oha+insulin	P	P	NPDR	A	A	126	172	7.8	2.3
66	tharasa	2268	50	f	46	4	oha	A	A	A	A	A	106	165	9.4	2.4
67	gowri	2307	70	f	60	10	oha+insulin	A	P	A	P	Microalbuminuria	146	189	10.5	1.6
68	meri	2335	63	f	46	17	oha	A	P	A	P	Macroalbuminuria	155	208	8.8	1.5
69	muniammal	2338	68	f	52	16	oha+insulin	P	P	A	P	Microalbuminuria	105	145	10.8	1.6
70	ambiga	2342	63	f	53	10	oha	A	P	A	P	Microalbuminuria	150	204	6.6	1.6
71	manoranjitham	2354	50	f	47	3	oha	A	A	A	A	A	118	165	7.5	2.2
72	mamta beevi	2360	62	f	43	19	oha	A	A	A	A	Microalbuminuria	140	175	11.6	1.5
73	shanta	2473	55	f	52	3	oha	A	A	A	A	A	96	155	6.4	2.2
74	indirani	2507	50	f	46	4	oha	A	P	A	A	A	135	160	7.4	2.2
75	chinnamani	2521	70	f	54	16	oha	A	A	A	A	Microalbuminuria	110	170	11.4	1.6
76	saroja	2530	65	f	47	18	oha	P	A	NPDR	A	Microalbuminuria	145	190	8.6	1.4
77	vairam	2540	65	f	49	16	oha	P	A	A	A	Macroalbuminuria	126	176	10.8	1.5
78	shanhakumari	2550	45	f	41	4	oha	A	A	A	A	A	98	140	10.6	2.2
79	rani	2555	45	f	43	2	oha	A	P	A	A	A	130	184	6.4	2.3
80	amaravathi	2554	60	f	50	10	oha+insulin	A	A	A	A	Microalbuminuria	160	205	8.4	1.6
81	tamilselvi	2867	55	f	47	8	oha+insulin	A	A	NPDR	A	A	130	166	9.6	2.4
82	rajathi	2572	44	f	42	2	oha	A	P	A	A	A	90	145	7.7	2.4
83	mariyayi	2595	43	f	41	2	oha	A	A	A	A	A	98	160	8.6	2.4
84	dhanalakshmi	26243	73	f	50	23	oha+insulin	P	A	NPDR	P	A	130	174	6.5	2.4
85	anjalai	26245	55	f	47	8	oha+insulin	P	A	NPDR	P	A	118	186	9.4	2.3
86	arokiyameri	26237	60	f	50	10	oha+insulin	A	A	NPDR	A	Microalbuminuria	110	185	10.6	1.5
87	jayaseeli	26240	75	f	65	10	oha	A	A	NPDR	P	Microalbuminuria	138	202	6.6	1.6
88	malarvizhi	2645	52	f	47	5	Oha	A	A	A	A	A	115	165	7.4	2.3
89	saroja	2667	58	f	48	10	oha+insulin	P	A	NPDR	A	A	106	144	6.4	2.4
90	pappa	2666	59	f	49	10	Oha	A	A	A	A	Macroalbuminuria	145	180	8.4	1.5
91	sebastiammal	2694	50	f	46	4	Oha	A	A	A	A	A	90	145	7.6	2.4

S.NO	NAME	HOSPITAL NO	AGE	SEX	AGE OF ONSET	DURATION(YEARS)	TREATMENT MODE	IHD	SHT	RETINOPATHY	NEUROPATHY	NEPHROPATHY	FBS+	PPBS	HbA1C	Mg
92	chellammal	2696	55	f	50	5	oha+insulin	A	A	NPDR	A	A	118	147	6.8	2.3
93	ranjitham	2691	60	f	50	10	oha	A	A	NPDR	A	Microalbuminuria	155	180	11.2	1.4
94	dhanalakshmi	2700	47	f	44	3	oha	A	P	A	A	A	95	165	5.6	2.3
95	chellammal	3902	55	f	50	5	oha+insulin	A	P	A	A	A	115	145	8.6	2.3
96	vatchala	4223	62	f	52	10	oha	A	A	NPDR	A	Microalbuminuria	140	180	7.4	1.6
97	ambigabathi	2707	58	f	50	8	oha	A	P	A	A	A	120	176	9.6	2.3
98	malarkodi	2708	60	f	45	15	oha	A	A	A	A	Microalbuminuria	110	190	8.8	1.5
99	saratha	2709	50	f	46	4	oha	A	A	A	A	A	100	173	7.6	2.4
100	padmavathi	2713	55	f	50	5	oha+insulin	A	P	A	A	A	90	155	5.4	2.4

ANNEXURE IV – KEYS TO MASTER CHART

A- Absent

F - Female

FBS - Fasting Blood Sugar

HbA1C - Glycosylated Hemoglobin

HTN - Hypertension

IHD - Ischemic Heart Disease

M - Male

Mg - Serum magnesium concentration

NPDR - Non Proliferative diabetic retinopathy

OHA - Oral Hypoglycemic Agent

PDR - Proliferative diabetic retinopathy

PPBS - Post Prandial Blood Sugar

P - Present

ANNEXUREV-PATIENT CONSENT FORM

Study detail : "STUDY OF SERUM MAGNESIUM LEVEL IN TYPE 2 DIABETES MELLITUS"

Study centre : THANJAVUR MEDICAL COLLEGE & HOSPITAL

Patients Name :

Patients Age :

Identification Number:

Patient may check (✓) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including haematological, biochemical, radiological tests. ☐

Signature/thumb impression:

Patients Name and Address: Place Date

Signature of investigator :

Study investigator's Name : Place Date

INTRODUCTION

India is frequently referred to as the diabetic capital of the world as it has the highest number of cases in the world.

In worldwide the last 2 decades, incidence is suddenly increased from 30 million cases in 1985 to 171 million in 2000. Recent data suggests that prevalence of DM by the year 2030 could be 360 million. DM is worldwide in distribution and the incidence of both types is rising.[1, 2]

The distribution of both T1 DM and T2DM varies worldwide, due to relative difference in genetic and environmental factors in different parts of the world. Recent data shows it is associated with 10-30% reduction of life

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INTRODUCTION India is frequently referred to as the diabetic capital of the world as it has the highest number of cases in the world. In worldwide the last 2 decades, incidence is suddenly increased from 30 million cases in 1985 to 171 million in 2000. Recent data suggests that prevalence of DM by the year 2030 could be 360 million. DM is worldwide in distribution and the incidence of both types is rising. 1, 2 The distribution of both T1 DM and T2DM varies worldwide, due to relative difference in genetic and environmental factors in different parts of the world. Recent data shows it is associated with 10-30% reduction of life expectancy, most common cause of blindness in the age group of 20...